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In 2012, 14 million people around the world were told that they had cancer. That year, 8.2 million people died of cancer, which is 1 in 6 of all deaths. Cancer is a word that sends shock waves through patients and family members. However, today more than half of the cancer patients in Belgium survive their illness. That is more than ever before.

Cancer is not one, but more than a hundred different diseases. Despite this, all these diseases have much in common: it always involves the uncontrolled growth of abnormal cells that ignore the signals and mechanisms that normally inhibit their growth. In most cases these cells penetrate adjacent tissues and spread to other organs.

Cancer can occur in any part of the human body. Breast, colon and lung cancer are the most common cancers in women. In men, prostate, lung and colon cancers occur most often. The survival chances of patients with cancer vary greatly, depending on the type of cancer and the stage at which the disease was diagnosed.

Cancer does not 'just happen'. It is a process that takes place in several steps and involves changes (mutations) in the DNA. These DNA changes lead to further changes that gradually transform the 'normal' cell into a cancer cell.

In this dossier we summarise ten of the changes that occur in cancer cells. They are the 'hallmarks of cancer' - the core of what we know today about the biology of cancer. However, there is still much that we do not know. That is why fundamental cancer research remains so important.

Cancer can affect anyone - young or old, female, male or child, rich or poor. However, because the risk of cancer increases with age, and because the population is ageing, the number of people with cancer - both in Belgium and worldwide - will continue to rise. And yet there is hope. The treatment outcomes of cancer are improving. The arsenal of medicines has increased significantly in recent years. Whereas in the past we were limited to surgery, chemotherapy or radiation, 'targeted' medicines are now available, along with blood vessel inhibitors, immunotherapy, etc. And there are many more new treatments in the 'cancer pipeline'.

What's more, we are now much better at detecting cancer at an early stage. All this increases the chances of a successful treatment. The Flemish government organises screening programs to detect breast, colon and cervical cancer at an early stage. For some forms of cancer there are even preventive vaccines available, such as for cervical cancer.

Furthermore, people can also take measures as individuals to prevent cancer. Almost half of all cancers can be attributed to lifestyle. Not smoking, preventing or reducing obesity, drinking less alcohol, a varied and healthy diet and more exercise: these are measures that we all know about because they are good for the heart and blood vessels, but they also reduce the risk of cancer.

Despite all that good news, and the jubilation you sometimes hear and read in the media about some new, spectacular treatment or cancer test, we are not finished with cancer yet. We cannot cure all patients, treatments are often accompanied by serious side effects and too many patients relapse after a number of years. Over the past hundred years, a great many chapters have been written about the textbook on cancer. But we are still far from the end of the story.

However, there is the hope that, in a not too distant future, we can turn cancer into a chronic, treatable disease. That would already be an incredible step for those millions of people around the world who were diagnosed with cancer in the past year.



The story of

KATRIEN VANDEROSTYNE

Katrien Vanderostyne, mother of two toddlers, discovered, quite by chance, a swelling in one of her breasts a year ago while in the shower. She had had a mammogram only two years before. "My 'baseline' measurement", she calls it. There was nothing wrong either. The gynaecologist had said: "You're now good for three years."

"When did those three years end?", Katrien asked herself that time in the shower. Unconsciously she started a self-examination, something she normally never does. "I discovered something hard. It will be nothing - that was my reasoning then and I did not pay attention to it." Eventually, however, Katrien made an appointment with her

general practitioner and then she stepped into a rollercoaster: "A day later I had a mammography and the day after that I saw the oncologist." "With children of five and three years old and a stepdaughter of sixteen, this hit me very hard", says Katrien. "I was 43, a marketing manager. I had a very busy professional life, a happy but lively family ... getting cancer was absolutely not on my roadmap."

"Suppose I did that self-examination two months later? Where would it have spread to then?"

Katrien's first reaction was sober, but hardly realistic: "I'll have a quick operation and I'll be back at work in two weeks. But the cancer turned out to be more aggressive and complex than I thought. The reality is that now, nine months later, I am still at home and my illness and rehabilitation programme will last a year."

Breast-conserving surgery was not an option for Katrien. "But I didn't think about that at the time. 'Cut out what has to go', was what went through my mind. That tumor had to get out of my body, and better tomorrow than the day after tomorrow." She got surgery. The entire tumour was removed, but the first axillary gland contained tumour cells. "The other glands luckily didn't", sighs Katrien, but the news had knocked her back: "Suppose I'd done that self-examination two months later.

Or I'd kept walking around with that tumour for weeks longer. Or was operated on later. Where would it have spread to then? That keeps gnawing away ... suppose ... suppose ... suppose ... I still have trouble with that."

The operation was followed by chemotherapy and then radiotherapy. "Chemo is an attack on your energy levels. There have been times when I felt miserable, I didn't get out of bed, I was very tired, but actually I realise that I have got off pretty lightly. I also knew that after the first two months I'd have the worst behind me. That thought helped me to pull myself together. We made a snip-off calendar with the children. After every 'magic potion' - that's what the children called chemotherapy - a piece could be snipped off. As a family, we've really taken that countdown to heart."

"I've never been someone to make a big thing of my appearance. But as soon as my hair started to fall out because of the chemo, things got very fraught. If your eyebrows and eyelashes fall out too, you really get that 'chemo' look. You stand in front of the mirror and don't recognise yourself. It's very confronting."

"Listening carefully to all experts around me and using all the aid you get offered as a cancer patient - that really helped me a lot. At the intake for the chemo there was a nurse who advised me to delegate everything that gave me no energy. Only do things that I found enjoyable and that replenish my energy levels. That advice was invaluable to me."





"Cooking soup and the kids, who helped me", Katrien laughs. "I threw myself into making healthy food and cooking - tons of soup and dozens of healthy salads. And then there was my family. Every day picking up the children from school. That might not be consistent with the vision I had for myself in life as a woman, but in those circumstances it gave me the rhythm I needed in my life. It gave me something I could pull myself up with." "I also realise that I'm extremely lucky to have a partner who has always been there for me and to have a strong social network. A neighbour who every now and then brought food, friends who sent me an encouraging message before a chemotherapy session ... small things, but they meant so much. "

"A neighbour who sometimes brought food, friends who sent me an encouraging message before a chemotherapy session... small things, but they meant so much."

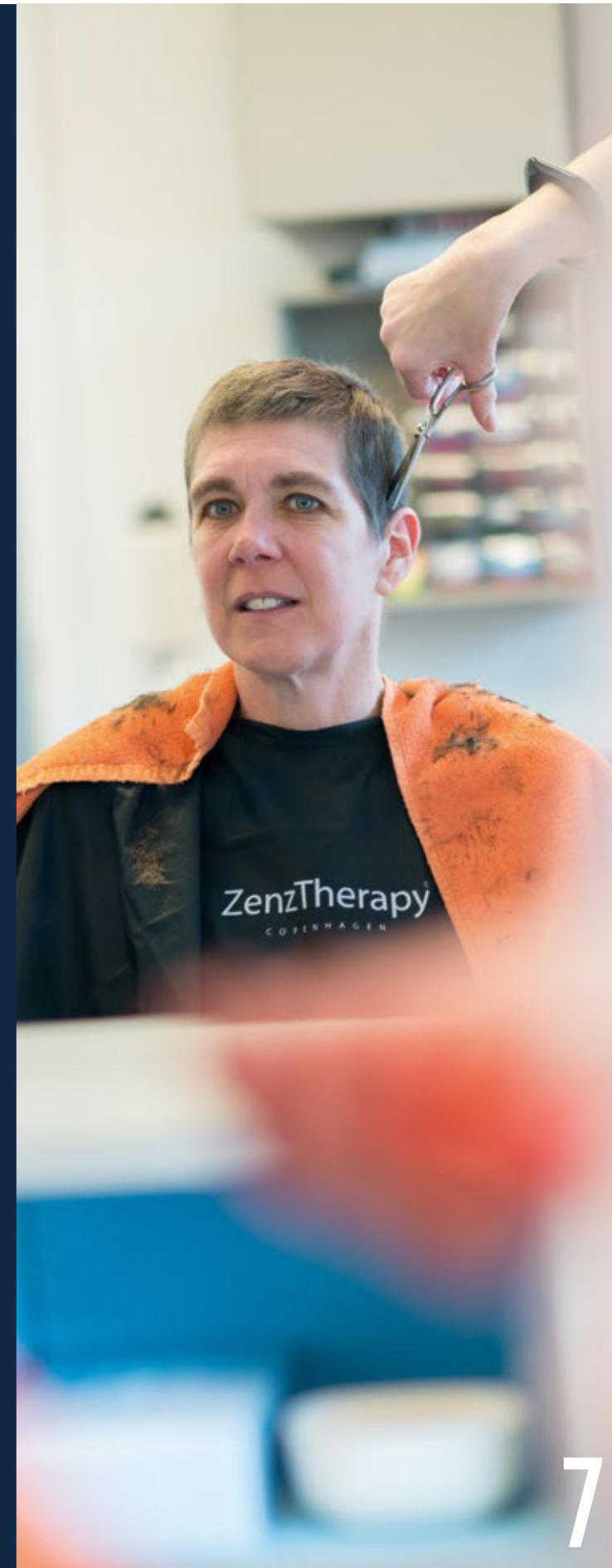
"I'm now in a rehabilitation program - aerobics and muscle strengthening exercises on Tuesday and fitness on Thursday. It's a bit of a tough regime really. But I have to rebuild myself as I'm not yet the Katrien I was before the cancer. I get tired much more quickly. I find it hard to deal with pressure. But I've always wanted to look forward, even in the darkest times. Although I have a fear

of throwing myself back into life completely. I still come up against limits that I didn't know about before. How will it be to go back to work? Maybe gradually, by working part time? ... these are still unanswered questions."

"My goal is to pick up the thread again. But I want to keep the good things that I've now built into my life."

"My cancer story is something that I carry with me. It is part of who I am now and will be in the future. My cancer journey was certainly not a 'cool' one, but there are people who have travelled much harder roads."

"My goal is to pick up the thread again", Katrien concludes. "But I want to keep the good things that I've now built into my life. I did a lot of sports before anyway. I want to keep it that way. I want to keep doing yoga, which I have just started. And eat healthily. Make time for the children ... and, above all, also get back in that stressful job. Why not? I need that drive. On the other hand, I realise that nothing is actually compulsory. Or at least, I have one 'must-do' for the year ... quickly get better and healthy again."



Uncontrolled cell growth

Colon cancer is different from lung cancer, breast cancer is different from leukaemia and prostate cancer is not the same as skin cancer. Even amongst breast tumours there are different types. And the same is true for lung cancer, skin cancer, leukaemia or any other kind of cancer. Cancer is an umbrella term for many different diseases. Every cancer is unique.

And yet ...

Regardless of which part of the body the growing tumour is in, one thing is constant - it always involves undesirable, uncontrolled growth and division of abnormal cells. Cancer cells have a competitive growth advantage over normal cells. Over time, they outgrow other cells and penetrate into the surrounding tissues. Without medical intervention, most tumours will eventually spread

to other organs and continue to proliferate there. This process is called metastasis (see 'From controlled to uncontrolled cell division').

Normal cells also divide and grow in a human body. But that process is strictly controlled. In the first place, normal cells only divide when they are stimulated to do so by growth factors.

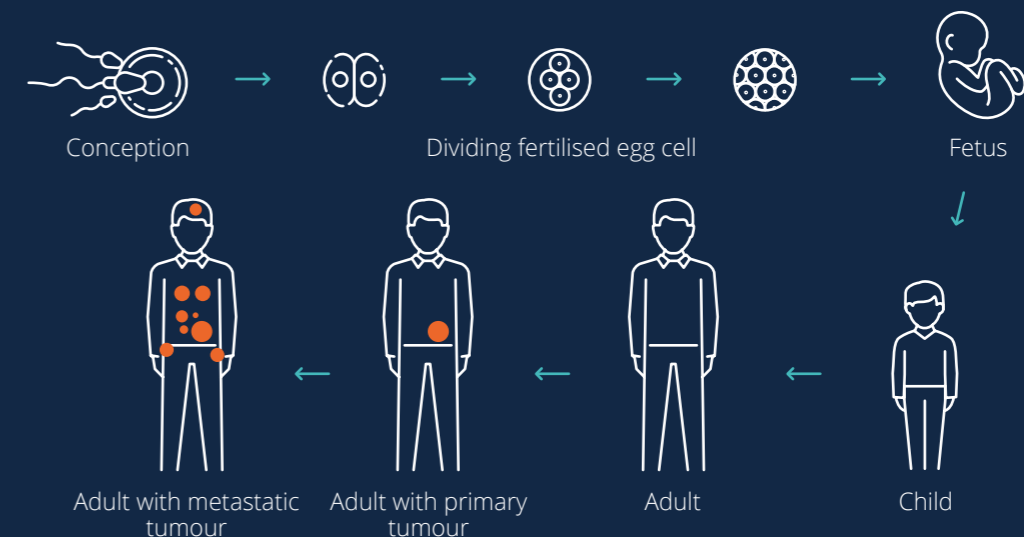
FROM CONTROLLED TO UNCONTROLLED CELL DIVISION

Everyone is the result of a sperm cell that fertilises an egg cell. The fertilised egg cell divides into two daughter cells, four granddaughter cells, eight great-granddaughter cells and so on.

From a certain stage, cells begin to 'differentiate'. That is, some cells become muscle cells, some become liver cells and others become skin cells or nerve cells. Slowly a person emerges, who grows, grows, and grows ... until he or she becomes an adult.

An adult human body has about 100,000 billion cells. They all come from that one fertilised egg. From very early on, cell growth and cell division are strictly regulated. That is why adults no longer 'grow'. Nevertheless, each 'mature' human body makes 50 billion new cells every day. Skin cells, for example, or blood cells, or cells lining the inside of the stomach or intestine.

Cancer cells (or tumour cells - we use the terms interchangeably in this dossier) break through all the control mechanisms that regulate cell division. They grow and divide uncontrollably and will eventually spread and grow in other parts of the body.



Furthermore, there are various mechanisms to slow down cell growth. For example, damaged cells, if they cannot be repaired for some reason, will undergo a form of programmed suicide, called apoptosis. In addition, cells have built-in mechanisms that allow them to divide only a limited number of times. Furthermore, cells are kept in check by their neighbours - they are dependent on blood vessels for the supply of oxygen and nutrients, and are 'supervised' by the immune system. Cancer cells, however, escape these growth restrictions and control measures.

The transformation of a normal cell into a cancer cell does not happen suddenly, but rather progresses stepwise and usually over many years. Step-by-step the tumour cell breaks out of the internal and external chains that limit its growth. Systematically, DNA changes accumulate (see 'DNA controls the cell from the cell nucleus') so that crucial genes and proteins no longer function properly, the growth engine is permanently in overdrive and all the brakes come off.

One chromosome from each pair comes from your biological mother and one from your biological father. These came together when the egg was fertilised by the sperm cell.

When a cell divides, each daughter cell receives the entire genome - all the DNA packages - from the parent cell. That requires the cell to do a lot of copying.

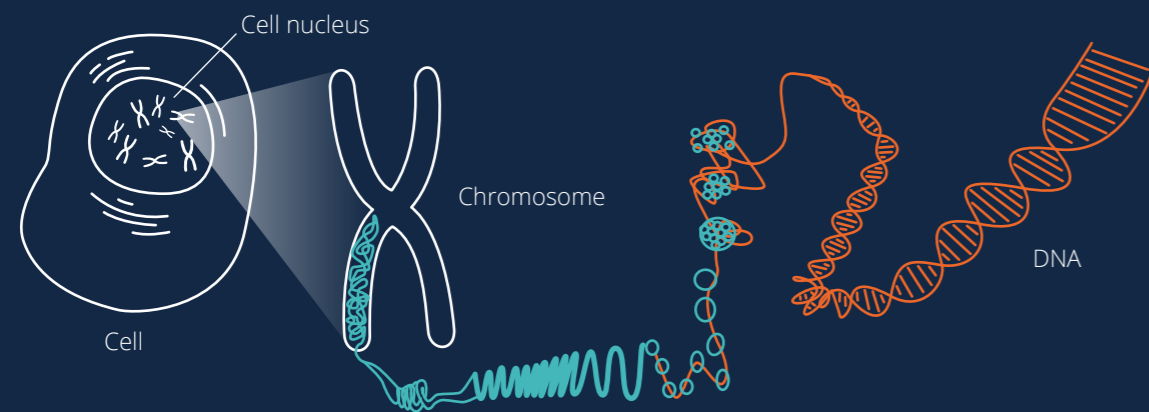
The DNA letter code consists of 4 building blocks represented by the letters A, T, C and G. The total genome consists of 3.2 billion of those letters which, if printed out, would fill 200 telephone directories.

A sequence of DNA letters encoding an 'instruction' is called a 'gene'.

Very often this instruction is the recipe for a 'protein'. In other words, the DNA code, or gene, is read and translated into a protein. Proteins are important in forming the structural parts of the cell, but also perform biochemical tasks. They ensure that we digest our food, move, see and hear the world around us, etc. Only 2% of the DNA effectively codes for proteins. The rest of the DNA is important for regulating the translation of instructions into proteins, the copying of the DNA, the maintenance of the structure of the DNA and the chromosomes, and so on.

Every now and then there is a mistake in the DNA copying. We call that a 'mutation'. An error in the code of a gene can lead to a defective protein. A number of these errors can eventually transform a cell into a cancer cell.

DNA CONTROLS THE CELL FROM THE CELL NUCLEUS



In the nucleus of each cell is the 'DNA', the menu containing the recipes for what a cell is and can do. The whole of the DNA in the nucleus is called the 'genome'.

DNA - a double-stranded molecule in the shape of a double helix - is densely packed in chromosomes. Each human cell has 2x23 chromosomes or 2x23 'packages of DNA'. If the chromosomes were to be unrolled and placed end-to-end, the result would be about 2 meters long with a diameter of 2 nanometres, or 2 millionths of a millimetre.

2 Social impact



Cause of death number 2

Cardiovascular disease is still the number one cause of death in Belgium. Cancer comes in at second place. About one man in three and one woman in four will have to deal with cancer before they turn 75.^{1,2}

- In Belgium in 2014 someone is told every 8 minutes that they have cancer: 35,950 men (53%) and 31,870 women (47%).
- On New Year's Day 2014, there were 331,776 people in Belgium who had been diagnosed with cancer between 2004 and 2013. That is 3% of the Belgian population. By then, many of them had been declared 'cancer free' by their doctors, while others were still fighting their illness every day.
- Every 20 minutes someone in Belgium dies of cancer, or about 27,000 people a year. 56% of these are men, 44% women.

These are dramatic figures. And it does not get any better. The Cancer Registry calculated that by 2025 the number of new cancer diagnoses in Belgium will rise to almost 80,000, or 17% more than in 2014. This increase is partly due to the increase in the population and to earlier and better detection of cancer, but also to ageing. Something else to be noted is that women are well on their way to overtake men. The increase in new diagnoses in men is 'limited' to 12%, but in women this has increased to 22%, because of the increasing number of smokers and thus lung cancers in this subgroup.

A disease of old age

Cancer can occur at all ages, but the figures clearly show, both in Belgium and elsewhere, that the risk of cancer increases significantly

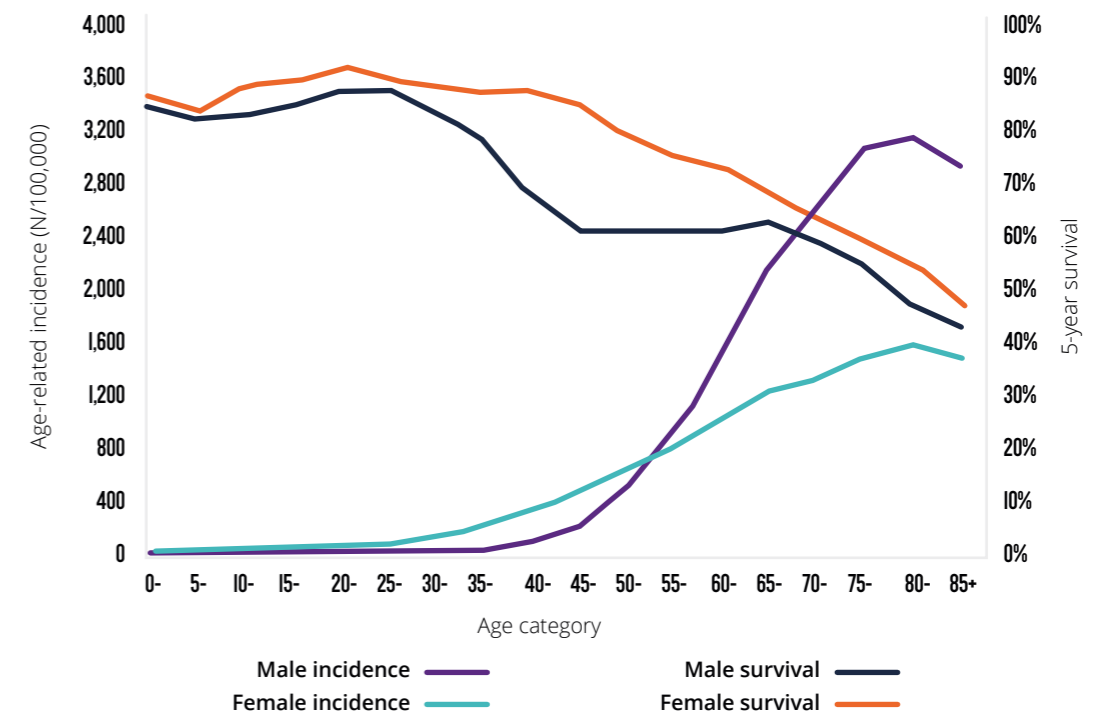


Figure 1. New cases of cancer in Belgium per 100,000 inhabitants and per age group in 2012, and 5-year survival per age category.^{1,2}
Source: Belgian Cancer Registry

with age. In Belgium, between two-thirds to three-quarters of all new cancer patients were 60 or older at the time of their diagnosis. In addition, the average survival rate also falls with age at diagnosis.

This is not in keeping with the stories in the media, which focus on young people or people at the peak of their professional lives. This leads to the perception that cancer occurs at least as often in young people as in the elderly. This is a complete misunderstanding.

Living longer with cancer

However, there is also good news: In Belgium, 59% of men and 69% of women are still alive five years after a cancer diagnosis. And that figure is increasing, year-by-year, and for all of the 10 most common tumours, both in men and women.

Admittedly, this increase has been achieved in small steps. Often not more than 0.5% and up to 2% per year, depending on the nature of the tumour. But it is those small steps that are important over the long term. That can be seen, for example, in the figures from the Scandinavian countries, which have been keeping a cancer registry for more than 50 years. In these countries the 5-year survival rate for all cancers in women increased from an average of 37.6% to 65.4% over the period 1966-2015. For men, the increase was even greater - from 26% to 65%.³

Major economic consequences

Every new cancer diagnosis leads first and foremost to an incalculable human suffering for the patients and their family, friends, acquaintances, colleagues and classmates..

In addition, there is also the economic price we pay for cancer. In 2010 we spent around 260 billion Euro worldwide on the treatment and care of cancer patients.⁴ These costs will probably increase, not only because the number of cancer patients is rising, but also because the costs of new treatments are high.

But that is only the tip of the iceberg. The economic consequences of cancer are not limited to the direct costs of treatment and care (by professionals). There is also the income that the patients lose due to their illness, the loss of work by family members who act as informal care providers. To this should be added the loss resulting from permanent disability or premature death.

The total cost of cancer - including direct and indirect care and social costs - is therefore estimated by the WHO at 970 billion Euro or 2% of the total gross domestic product (GDP) of the world (in 2010). To put this into perspective, this corresponds to the combined GDP of Belgium, Austria, Denmark and Finland.⁵

CANCER IN THE WORLD

IN 2012 **14 MILLION** PEOPLE WERE DIAGNOSED WITH CANCER

ONE DIAGNOSIS EVERY 2 SECONDS

8.2 MILLION PEOPLE DIED THAT YEAR FROM CANCER. IN 2015 THIS HAD ALREADY INCREASED TO 8.8 MILLION



NEARLY 1 IN 6 GLOBAL DEATHS

IN 20 YEARS' TIME THERE WILL BE **1.7 TIMES MORE CANCER PATIENTS** THAN THERE ARE TODAY



ABOUT 70% OF ALL DEATHS FROM CANCER OCCUR IN LOW- AND MIDDLE-INCOME COUNTRIES. HOWEVER, THE CHANCE OF GETTING CANCER IS THE HIGHEST IN DEVELOPED COUNTRIES.

**NORTH AMERICA
WESTERN EUROPE
AUSTRALIA
NEW-ZEALAND
ARE ON TOP
IN CANCER INCIDENCE**



MALES THE MOST COMMON:
LUNG CANCER (16.7%)
PROSTATE CANCER (15%)
COLORECTAL CANCER (10%)
STOMACH CANCER (8.5%)
LIVER CANCER (7.5%)



FEMALES
BREAST CANCER (25.2%)
COLORECTAL CANCER (9.2%)
LUNG CANCER (8.7%)
CERVICAL CANCER (7.9%)
STOMACH CANCER (4.8%)



THE MOST DEADLY:
1,690,000 LUNG CANCER
788,000 LIVER CANCER
774,000 COLORECTAL CANCER
754,000 STOMACH CANCER
571,000 BREAST CANCER



CANCER COSTS THE WORLD 2% OF ITS BBP OR ALMOST

1,000 BILLION EURO EVERY YEAR



Source: World Health Organization (WHO), 10 facts about cancer - www.who.int/features/factfiles/cancer/en/

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The story of

DIRK VELDEMAN

Dirk Veldeman walks 6 to 8 kilometres every day, through woods and fields, and preferably in places where he is not allowed to go. The tumour in his blood hasn't undermined his headstrong and adventurous character. "It may have tempered it, but that can also be caused by age", jokes the energetic octogenarian. Dirk immediately

wanted to talk about his cancer story. Being on the other side of the microphone ... as a retired Belga journalist it's somehow different, you see him thinking.

Eleven years ago, a blood test showed that Dirk had Waldenström's disease. That is an abnormal

maturation of white blood cells in the bone marrow. For many years Dirk had only to see the doctor for check-ups and wait to see how the disease developed. Five years ago there were signs of anaemia. A mild course of chemotherapy pepped him up again. A year later a kidney tumour appeared. That was successfully removed. Two years ago, the verdict was large B cell lymphoma, after a swelling in his throat was detected. Two courses of chemotherapy, radiotherapy and a stem cell transplant followed. "I was in and out of the hospital for a whole year," says Dirk. "From one therapy to another. You feel your body breaking down. But you don't have much choice."

"Many people have a hard time listening to your insecurities, your grief, your doubts, your frailty. The stigma of cancer - it is still there."

"In my head I have been living with cancer for eleven years, from the moment Waldenström's disease was diagnosed. But I have always tried to continue my normal life. Even between my chemotherapy sessions. Only on the eve of the stem cell transplant with my own bone marrow cells did I realise 'If this doesn't work, it's over'. That was the most confrontational moment of my entire treatment. Then I made an assessment of what I'd done with my life. Whether there was something I should regret. Whether it had been worth it. For myself and for others."

"Cancer is still a taboo subject. No matter how you look at it. People often don't know how to deal

with you as a cancer patient. While your social network is just as important for getting you through it. People who live with cancer get to know very well who they can count on and who they can't. And yet I do not blame anyone. Many people struggle with fear and unfamiliarity when dealing with the disease and the sick person. They have a hard time listening to your insecurities, your grief, your doubts, your frailty. The stigma of cancer - it is still there."

After his stem cell transplant, Dirk followed a rehabilitation programme at KanActief. Together with a group of 12 cancer patients whose treatment had been largely completed. "Aerobics - not an obvious pastime for someone aged 70", laughs Dirk. "Movements I hadn't done for 20 years, and certainly not in an aerobics outfit". But there's also the contact with people who, just like you, are trying to pick up the threads again after a major cancer treatment ... that is so important. The solidarity you get in a group of fellow sufferers is indescribable."

"The improvement of my physical condition, due to the rehabilitation programme, also gave me a mental boost. But above all: the program ensures routine and a daily rhythm. A routine that I controlled and managed myself. Remember, I came out of a treatment process in which everything was planned and done for me. I had literally been an object that was no longer able to make decisions about my own life. That was very far-reaching. When to go to sleep, eat, get medication, see people ... everything was laid out. And on the day the doctors say the treatment is over, you fall out of that protective cocoon, which had been built around you with the best intentions."





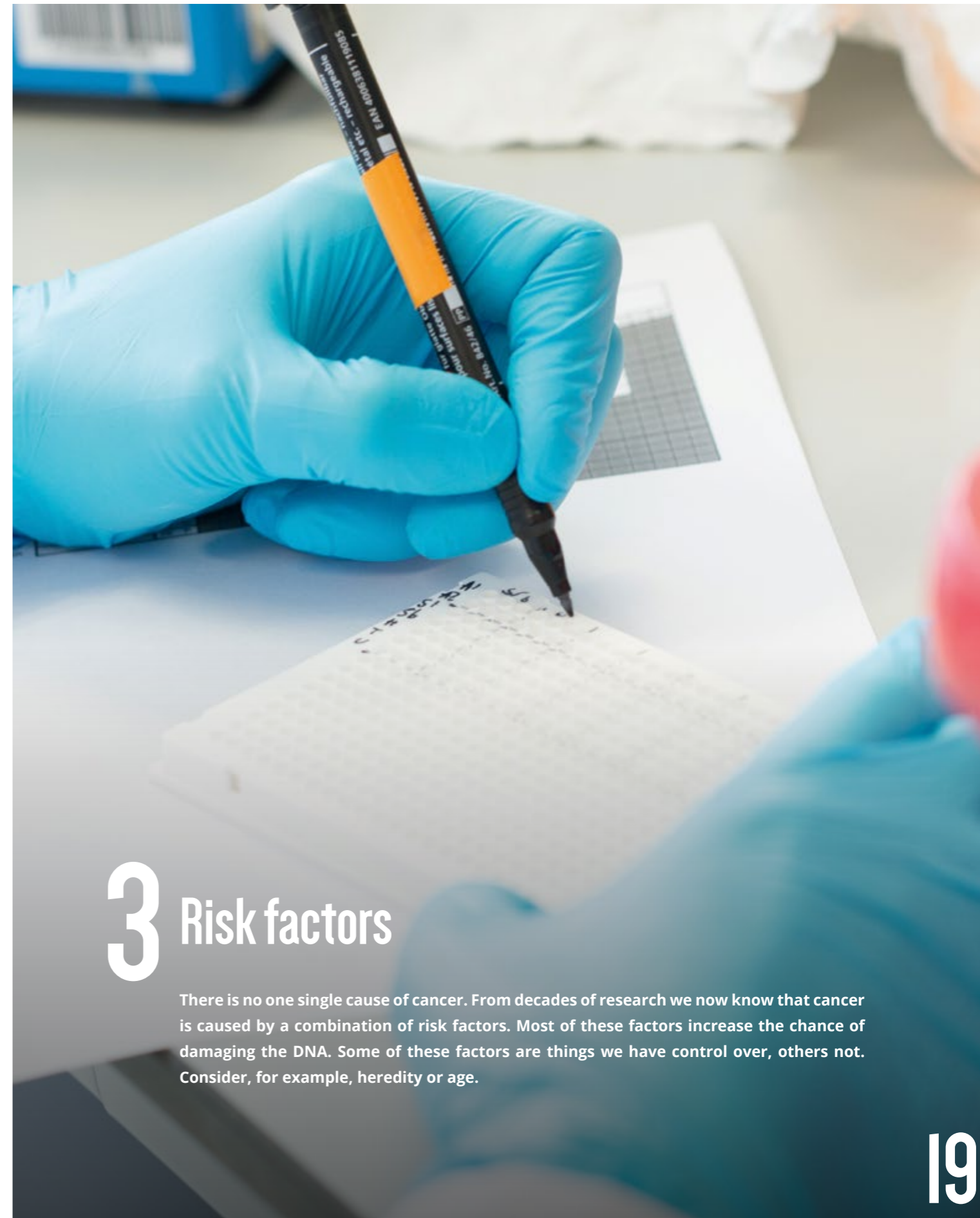
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"With a rehabilitation program such as KanActief, this transition is more gradual. Once again, you are building-up rhythm and structure - after all, you have to participate in that program two or three times a week. But this time it's of your own free will and free choice. A big difference with the medical program." "Rehabilitation programs for cancer patients must be an integral part of any cancer treatment", says Dirk. "Now it is something added without any obligation. In fact, every cancer patient should be able to participate."

"After my cancer treatment, I allow myself to be bored every now and then. I could not do that earlier. I always looked for something to keep me busy. Now I can just stand still - literally in fact - and ponder the things of everyday life. Not to complain and to say how bad it all is. On the contrary. It's more like enjoying a newly-furnished life."

Furnished with the knowledge I had from before my treatment, but with a new form of creativity and openness. Seeing things that I never saw before. Stopping to consider things that I didn't even notice in the past. Even in relationships with people, especially with my wife. Yes, I've begun a new life. Absolutely. You know, I often think about that, and actually I feel that those stem cells have given me that new life. I was completely broken down, but now, I am rebuilt."

"Now I can just stand still - literally even - and consider everyday things. Not to complain and to say how bad it all is. On the contrary. It's more like enjoying a newly-furnished life."



3 Risk factors

There is no one single cause of cancer. From decades of research we now know that cancer is caused by a combination of risk factors. Most of these factors increase the chance of damaging the DNA. Some of these factors are things we have control over, others not. Consider, for example, heredity or age.

Genetic predisposition

In a small minority of cancer patients, inherited errors in the DNA (from their biological father or mother) lead to a greatly increased risk of cancer. The best known familial or hereditary cancers are breast cancer, ovarian cancer and colon cancer. But even for these types of tumours, the inherited forms are in a minority. For example, changes in the BRCA1 or BRCA2 gene (the 'Angelina Jolie' form of breast cancer) represent an estimated 5 to 10% of all breast cancers.

Age

The older you get, the greater the risk of cancer (see Figure 1 on page 13). Simply put, because we accumulate more and more errors in the DNA as we get older. In addition, the immune system of elderly functions less well, so that abnormal tumour cells are detected and destroyed less efficiently.

Toxic substances

Some chemicals are carcinogenic. Think of asbestos, aromatic hydrocarbons from soot or tar (in cigarettes for example, but also exhaust fumes), aflatoxins (produced by fungi on food products), benzene (solvent), cadmium and other heavy metals.

A weakened immune system

People whose immune system is undermined by an infection of the immune cells (such as HIV) are at a higher risk for some forms of cancer. Transplant patients - whose immune system is suppressed with medication to prevent rejection - are also at increased risk of cancer.

Hormone replacement therapy

The use of female hormones can alleviate menopausal symptoms, but also has disadvantages. Depending on the type of

treatment, the dose and the duration, it increases the risk of blood clots, heart attacks, strokes, breast cancer and uterine cancer. With long-term use (more than 10 years) there is a slight increase in the risk of ovarian cancer.

Radiation

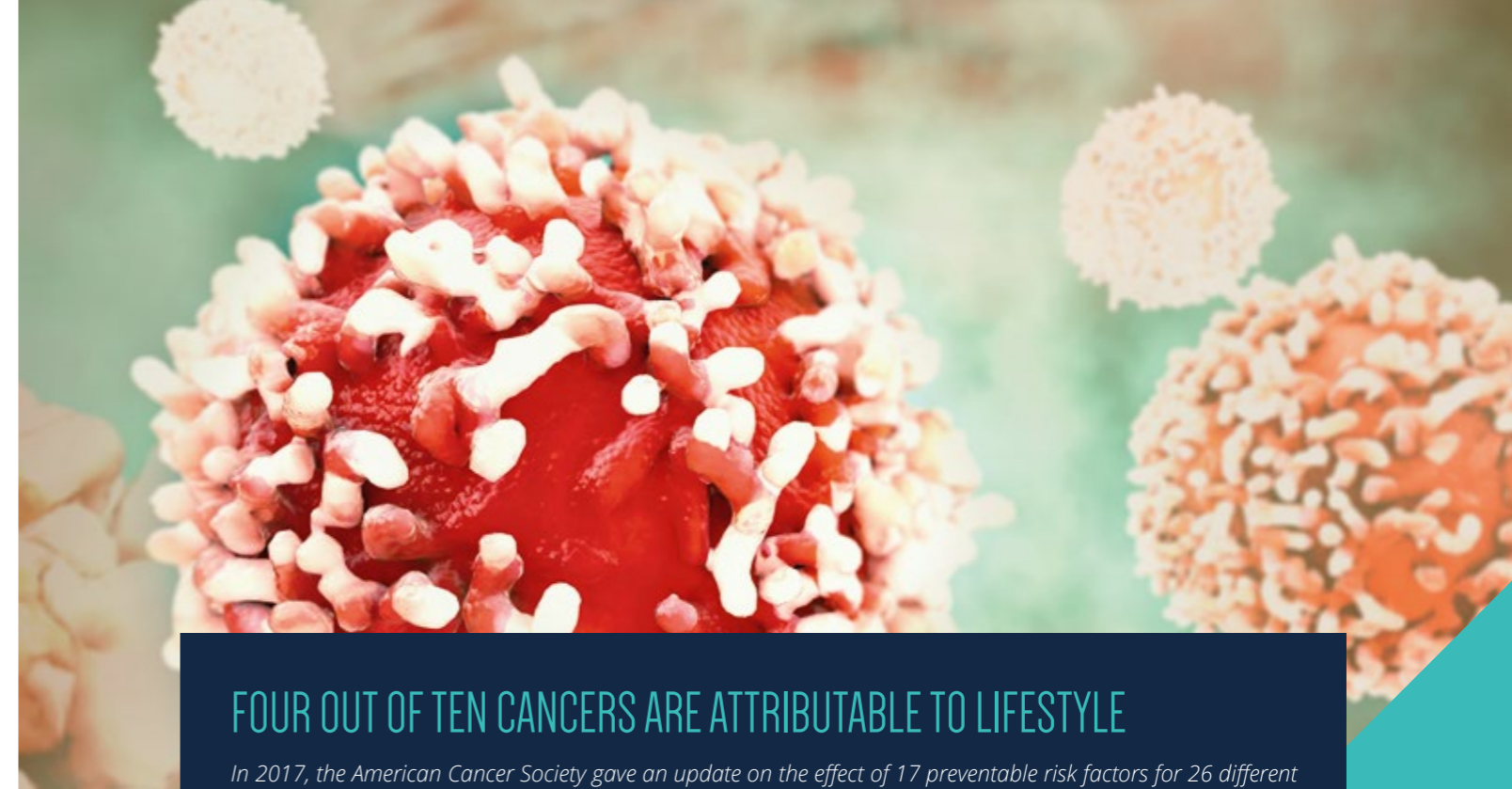
Ultraviolet light, X-rays and ionising radiation cause breaks in the DNA of cells that are exposed to them. The risk of cancer is determined by the frequency and duration of the exposure, and by the amount and type of radiation.

Viruses and bacteria

Although the great majority of infections with bacteria and viruses do not lead to cancer, there are some exceptions. The human papillomavirus (HPV), for example, can cause cervical cancer and head and neck cancers. Chronic infections with hepatitis B or C viruses increase the risk of liver cancer. The bacterium *Helicobacter pylori* causes inflammation of the gastric mucosa, which can, over time, lead to stomach cancer.

Lifestyle

Smoking, alcohol, obesity, a sedentary lifestyle, some foods ... they all increase the risk of cancer (see 'Four out of ten cancers are attributable to lifestyle'). People who live healthily, eat a varied diet, get enough exercise, drink with moderation, pay attention to their weight and don't smoke, reduce their risk of cancer.



FOUR OUT OF TEN CANCERS ARE ATTRIBUTABLE TO LIFESTYLE

In 2017, the American Cancer Society gave an update on the effect of 17 preventable risk factors for 26 different cancers.^o The figures refer to the US, but largely apply to Europe as well.

Smoking alone accounted for 28.8% of all cancer deaths in 2014. No less than 81.7% of lung cancers were due to smoking, in addition to 73.8% of laryngeal cancers, 50% of oesophageal cancers and 46.9% of bladder cancers. Fourteen different types of cancer are more common in smokers than in non-smokers.¹

These figures are striking: more than 8 in 10 patients with lung cancer are smokers or have smoked. Lung cancer is also one of the deadliest cancers: 80% of patients die within 5 years of diagnosis. Non-smokers, on the other hand, rarely get lung cancer. Although (passive) smoking is still a risk!

In addition to smoking, there are also important effects from overweight/obesity, (7.8% of total cancer cases and 6.5% of cancer deaths), alcohol (5.6% and 4.0% respectively), insufficient fruit and vegetables in the diet (5.9% and 2.7%) and physical inactivity (2.9% and 2.2%). Lack of dietary fibre and calcium, or an excess of processed meat products and red meat each contribute less than 1%.

In conclusion, in 2014 about 42% of all cancers and 45.1% of all cancer deaths were due to risk factors related to lifestyle. That does not mean, however, that all these tumours are really avoidable. There will always be colon cancer, lung cancer or liver cancer, but the number of cases could be significantly lower. Nor does it mean that we have to burden patients with a sense of guilt and/or make them feel responsible for their tumour. What it does mean is that we need to make people aware of the importance of a healthy lifestyle, that we can expect the government to pursue a policy that focuses on health and prevention and that we must strongly support any initiative to achieve this.

4 Research leads to new insights

As recently as in the mid-1970s, the mechanisms behind cancer were a total mystery. Despite half a century of cancer research, there was little insight into how the condition developed, how cancer cells ignored signals and mechanisms that slow the growth of normal cells, why they succeeded in penetrating adjacent tissues and how they metastasised.

Until a few adventurous researchers began 'molecular' cancer research. It was initially met with scepticism, because cancer was thought to be too complicated to be understood by simple molecular mechanisms ... At least that was the opinion of many of the then 'established' cancer researchers. But molecular biologists soon unleashed a true revolution in cancer research.⁷ They succeeded in charting the molecular properties and steps that transform a normal cell into an aggressive and uncontrollable cancer cell.^{8,9,10}

We outline below 10 of the characteristics that determine why cancer cells are better adapted to survive and reproduce faster than other cells. And why they spread at one time rather than another and look for other organs where they can start another growth spurt. These hallmarks constitute the signature or the 'true face', as it were, of the cancer cell.

The hallmarks of cancer



1. A growth engine running permanently at full speed

Normal body cells only divide if they receive an external growth signal. This could be a hormone or a growth factor, for example. Cancer cells, however, no longer need that external stimulus to divide. They have locked one or more growth switches into the 'on' position so that the growth engine does not stop. It is as if the accelerator pedal in your car is fully depressed. Researchers and cancer physicians call these growth switches 'oncogenes'.



2. Broken brakes

Cells have internal and external mechanisms to slow their growth and division or even stop them completely. These processes are orchestrated by proteins that we call 'tumour suppressors'. In cancer cells more and more of these mechanisms are disrupted by an accumulation of errors in 'tumour suppressor genes'. This undermines their growth-suppressing capacity. It's as if you're driving down the mountain in a car with broken brakes.



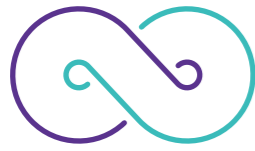
3. Reduced DNA repair and defective chromosomes

The accumulation of DNA changes accelerates in cancer cells as the disease progresses. This is caused by damage to the genes and proteins responsible for protecting the DNA and/or repairing DNA errors. As a result, advanced cancer cells are often characterised by the presence of massive mutations or other genetic abnormalities in which chromosome fragments or even whole chromosomes are duplicated and others appear to be torn.¹¹



4. Programmed cell death switched off

When normal cells become too badly damaged, they activate a self-destructing mechanism. This process is called programmed cell death or apoptosis - a form of cellular suicide. For example, if your skin is burnt by the sun, it sloughs off. This is an example of apoptosis. Cancer cells are able to switch off the mechanism for programmed cell death.¹²



5. Eternal life

Cells have a limited potential for growth. They can only divide 60 to 70 times. The end pieces of the chromosomes, called telomeres, are responsible for this. With each cell division, these telomeres become shorter until there is too little of them left. The chromosome then becomes unstable. Cancer cells escape this growth limitation by activating the proteins that make telomeres longer again.



7. Alternative fuels and building materials

Sugars are an important nutrient for cancer cells as much as for normal ones. However, cancer cells change their metabolism and ferment their sugars instead of completely breaking them down to CO₂ and water, as most cells do. Although fermentation supplies less energy, it does generate intermediates such as pyruvate that can be used as building materials for new proteins and DNA.¹⁴



9. Invasion and metastasis

One of the key features of cancer cells is their ability to invade neighbouring tissues (invasion) and to spread (metastasis) to other parts of the body. This capacity for invasion and metastasis is the biggest difference between 'benign' and 'malignant' tumours. In many cases, it is the metastases that are fatal for the patient.

Knowledge in full (r)evolution

Increasing complexity

The 10 characteristics of cancer outlined above build on what are called the 'hallmarks of cancer', a concept that was proposed in 2000 by cancer researchers Robert Weinberg and Douglas Hanahan. The 'hallmarks' are important pieces of the cancer puzzle. They were used for many years as a frame of reference to put medical and scientific knowledge about cancer into context.

But it became clear that the whole cancer puzzle is far from complete. The old answers have given rise to new questions. Often difficult and complex questions. With cancer, we are still a long way from the end of the story.

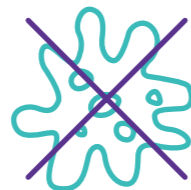
Below is a limited sample of the numerous chapters that are still missing from the cancer story, and which have come to the attention of cancer researchers in recent years:^{20,21}

- **Tumour dynamics** – There is a tough problem involving the complex multi-stage cancer process. We often talk about that process as if it took place in discrete steps and phases that can easily be distinguished from each other. In reality, tumour growth is a continuous and evolutionary process, with different biochemical and cellular mechanisms that interact with each other. The sequence of these mechanisms and how they interact is nowhere close to being clearly understood.
- **Inter-tumour and intra-tumour heterogeneity** - Within a tumour type, and even within one and the same tumour, there is a whole range of subpopulations of cancer cells. These subpopulations or 'subclones'



6. New blood vessels

The process by which new blood vessels are formed is called angiogenesis. These blood vessels carry oxygen and nutrients to the cells. A growing tumour also needs new blood vessels to supply its cancer cells. Tumours therefore succeed in transmitting signalling substances so that new blood vessels grow in the direction of the tumour and even into the tumour.¹³



8. Defences bypassed

Certain types of white blood cells scan our body for nascent cancer cells and try to eliminate them. They monitor (the term 'surveillance' is often used) every cell that threatens to exhibit malignant characteristics. Cancer cells manage to mislead these immune cells.¹⁵



10. Chronic inflammation

Inflammation is a complex biological response to harmful stimuli. An inflammatory reaction consists of a combined action of molecular signal substances, immune cells and blood vessels. Sometimes an inflammatory response runs out of control and becomes chronic. Recent epidemiological studies indicate that at least 20% of all cancers could be a direct result of chronic inflammation.^{16,17} In addition to initiating tumours, inflammation also plays a decisive role in their growth and spread.¹⁸ A cancer researcher has put it like this: "If genetic damage is the match that ignites the fire of cancer, chronic inflammation is, perhaps, the fuel that continues to feed the flames."¹⁹

have partly undergone a common development and partly gone their own way. In other words: they differ from one another on a genetic level, have different growth characteristics and, therefore, also have other competitive advantages. This diversity of subpopulations is one of the key reasons why tumours adapt relatively quickly to changing circumstances – for example, the presence of an anti-cancer drug. Resistant subpopulations, possibly present only in a small proportion in the tumour at the start of treatment, can quickly gain the upper hand over other populations. In addition, the various subpopulations in a tumour work together. In other words, a tumour has to be seen as a community of groups of cancer cells, each with its own history and its own contribution to the tumour.

- **The tumour microenvironment** - Finally, there is the increasing insight into the role of the tumour microenvironment. Over the past decades, cancer research has mainly focused on the tumour cell itself. However, it is becoming increasingly clear that there are many interactions between the tumour cell and the other cells in its environment. Take the example of metastatic cancer cells. They end up in a new, unknown, inhospitable, even downright hostile environment. Nevertheless, a number of them manage to develop a competitive growth advantage in these foreign tissues. For the first time we are learning how they adapt to this new environment and how they can manipulate other cells to their own advantage.

Systems biology and big data

In short, the focus of cancer research is shifting from 'the cancer cell, in one particular phase, in one specific place' towards 'the whole of the tu-

mour, in its full diversity and dynamic development and in connection with its environment'.

This calls for an extension of the traditional molecular research approach which some called the 'one gene, one protein, one property' approach. This approach was particularly useful in the past since it led to entirely new insights into cancer, and to faster diagnoses, better prevention and new medicines, as will be explained in the following sections. However, we have now started a new research phase that is based on an integrative or systemic approach to cancer. With new research tools, new methods and, at the same time, new challenges. An important component of this system-orientated approach is genomics and its derived 'omics' technologies. Genomics means investigating the entire DNA in a tumour. Today, the complete pattern of all DNA changes is being mapped worldwide in thousands of tumours. Some centres have already succeeded in doing genomics up to the level of a single tumour cell (called single cell genomics), which is useful for mapping-out the presence of subpopulations.

Thanks to this technology, we can today compile extensive catalogues of the genetic changes that tumour cells undergo.^{22 23 24}

However, it's not just a matter of genetic changes. We are also increasingly able to visualise the totality of RNA molecules and proteins in a tumour via what are called transcriptomics and proteomics. In addition, we are able to form a picture of the entire biochemical and metabolic reactions in a tumour (metabolomics). This sort of high-tech research does not have to be limited to the tumour cell, but can be extended to the cells in the neighbourhood of the tumour.

An enormous amount of data is generated by 'omics' research and related disciplines. Scientists and physicians from different disciplines work closely together to manage, analyse and integrate the complex and extensive data sets resulting from these disciplines. It is clear that computer power, bioinformatics and, perhaps increasingly, artificial intelligence are involved in this. These and other innovations in the cancer research field - think, for example, of more powerful microscopes and new imaging techniques - open up wholly new research perspectives. They will be needed, too, if we want to understand cancer in all its aspects.

Stefan Gijssels

"The governments of Europe spend a combined total of 715 million Euro each year on non-commercial cancer research; 143 million Euro of this goes to new treatments, while the rest is for basic research. Some people would call that a huge amount. Well, in my view that's peanuts, especially when you compare it with what cancer costs society. So far, too little money is spent on basic research. Not only for cancer, but also for other diseases, such as Alzheimer's disease."

Dirk Veldeman

"Cancer research is developing rapidly. A lot of money goes to research. And rightly so. But you can't always expect immediate results from research. That's not how it works. In addition, many new treatments are discovered by chance. Penicillin, for example. But if you don't explore, you can't find something by chance, can you?"

More research than ever before

Cancer research is running at full speed. In 2017 alone 165,000 articles were published in the medical and scientific literature containing research results on cancer. That means 450 articles per day, or one article every three minutes.

There was not much less published in the years prior to this either. Between 1 January 2013 and 31 December 2017, 810,000 scientific articles on cancer were published. Not so long ago, in the period 1995-2000, for example, there was only a third of that number of articles.

No other medical topic comes close as far as research efforts are concerned. Hundreds of laboratories all over the world and thousands of hospitals continue their fight against cancer every day.

EXPERIMENTAL ANIMALS IN CANCER RESEARCH

Necessity

In a large part of the cancer research no experimental animals are used. Instead, experiments are performed in test tubes or on cell cultures (in vitro research), or the research consists of clinical studies, or epidemiological or care-oriented investigations. Despite this, research on laboratory animals (in vivo research) is not only important, but even inevitable if we want to understand cancer and develop effective treatments. A small sample of the numerous examples, some with a historical touch, that illustrate how research on laboratory animals has yielded benefits for cancer patients:

1. In 1918, the Japanese researcher Katsusaburo Yamagiwa smeared a tar-like substance from coal onto the ears of rabbits.^a The rabbits then developed skin cancer. This confirmed the hypothesis of the British physician Percival Pott who in 1775 claimed that scrotum cancer - something that only occurred in chimney sweeps - was caused by a carcinogenic substance present in chimney soot.
2. The Rous sarcoma virus (RSV), a retrovirus that can cause cancer, was first discovered in chickens.^b That discovery led to the identification of the *src* oncogene and all subsequent oncogenes in animals and humans.^c
3. Why some metastatic cancer cells have a preference for liver, lungs or brains was discovered by injecting cancer cells from a melanoma (an aggressive form of skin cancer) into mice.^d
4. The crucial importance of VEGF (vascular endothelial growth factor) during embryonic development was first demonstrated in mice.^e VEGF is a substance secreted by cancer cells that causes blood vessels to grow into and within the tumour. Anti-VEGF drugs should not be given to pregnant women because of the danger to the foetus, as was shown in the mice.
5. That the metabolism of macrophages - a specific type of white blood cell - is important for the correct growth of tumour blood vessels and plays a role in the formation of metastases, was first established in mice in which certain genes were switched-off (known as 'knockout mice').^f
6. Using a mouse model, researchers were able to prove that melanoma originates from mature pigmented melanocytes that 'de-differentiate'.^g

Well-considered assessments

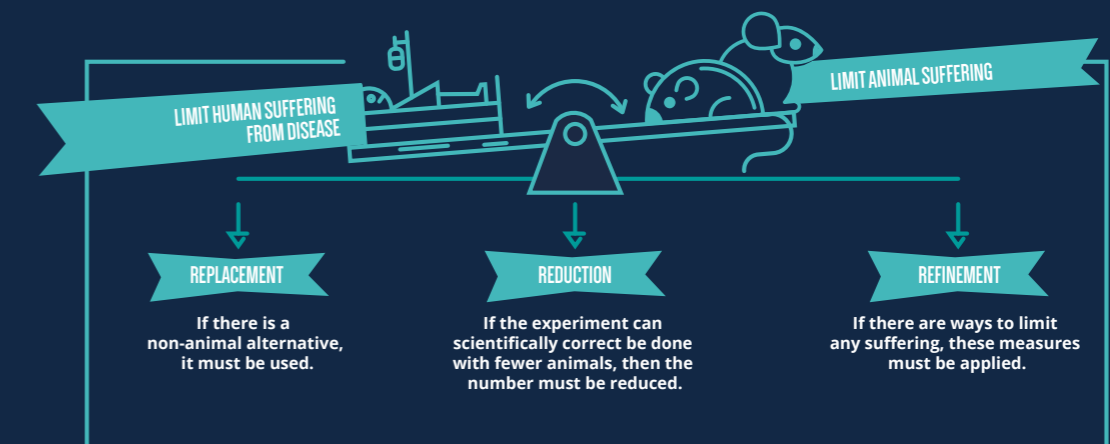
Researchers conduct experiments on animals only after thorough consideration. For every new project, they carefully weigh the use of laboratory animals against its importance for human health. In addition, maximising animal welfare comes at the top of the list of priorities:

- Researchers may only work with laboratory animals if they are trained in animal welfare and the ethical use of laboratory animals in experiments.^h
- Animal experiments can only be started if they have the approval of the 'animal testing ethics committee' of the university concerned. To get this approval, researchers must argue why they need animals for the research, describe in detail the experiments to be carried out, say how many animals will be used (and why so many are needed) and demonstrate that the experiments have not already been performed.
- Researchers are expected to strictly apply the 3R principle:ⁱ replacement, reduction and refinement of animal experiments. In concrete terms, this means that they must strive to replace animal experiments as far as possible with experiments in test tubes, with cell cultures or with computer models. Furthermore, they must

limit the number of tested animals to an absolute minimum and perform the experiments in such a way that animal suffering is reduced as far as possible and so that animal welfare is maximised. The animals used must also be those with the lowest possible level of consciousness: if an experiment gives the same information in fruit flies as in mice or rats, the researchers must invariably use the fruit flies.

There are important medical and scientific questions that doctors and researchers can only answer through research on living animals in which all complex interactions take place between cells, tissues and organs. It cannot be emphasized enough that research with laboratory animals is now one of the most heavily regulated research activities. It is often thought that this research is performed on monkeys, cats and dogs, but the most commonly used laboratory animals are, in fact, mice, fruit flies and zebra fish, which are grown specifically for research. The animals are housed in the best conditions. Their welfare is even registered individually (e.g. in mice) and monitored. Obviously, this leads to a significant additional expense for the laboratories. This is one more reason why researchers are as 'economical' as possible with laboratory animals and only use them when there really are no alternatives.

Well-considered animal research therefore has its place in the search for cancer treatments. This is a position also held by leading patient organizations and organisations that support cancer research.



SG

The story of

STEFAN GIJSSELS

Stefan Gijssels was Vice President Communication & Public Affairs at Janssen Pharmaceutica. He was responsible for the Europe, Middle East and Africa region and had just guided his department of 66 people through a reorganisation and consolidation phase. Stefan: "At first there was a suspicion of appendicitis, but a few months later a

colonoscopy revealed colorectal cancer. The discussion with the oncologist was reassuring: it was starting stage so surgery would do the job, 90% chance of survival, nothing to be worried about ... ". The calendar is open at Spring 2015. "However, the keyhole operation was stopped half-way through. It was much worse than expected."

"Apart from the colon, also the small intestine was affected. There were metastases everywhere. Suddenly the doctors started talking about stage IV colorectal cancer. I would have to be opened up completely. On the Internet I found that, with this diagnosis, my chances of survival had fallen to 10%. From 90% to 10%. That was hard to swallow. Certainly for my wife and children."

"Seeing what happens emotionally to the members of your family is the most important side effect of cancer."

"I underwent a very heavy operation," says Stefan. "Not only did the surgeon remove all tumour tissue from my intestines, my abdominal cavity was also 'rinsed' with heated cytostatics to deal with any remaining tumour cells. When you wake up, you feel like an organ lying on a bed. On one side, you're full of tubes. They pump all kinds of fluids into your body. On the other side, tubes allow other fluids to drain out. I was like that for two weeks. Heavily numbed. In the first five days I was able to stay awake, with difficulty, for a few hours. After two weeks I could go home, but I was totally helpless and powerless. I didn't even have the strength to turn over in bed."

"As the weeks progressed, it started to improve. Although I wasn't spared from complications. And then I got six months of chemotherapy. Every two weeks on the Monday a visit to the day clinic for a new chemo pump and then back home. The longer the chemo went on, the more trouble I had with it. On some days I would throw up a lot and be totally drained of energy. On other days I could walk for an hour or two. Often with friends. Speaking for hours with people who care about you. That really helps."

"The worst thing about cancer is what you see in the eyes of your partner, your children or your parents", Stefan remarks. "I look at my wife and I see the fear in her eyes. When I phoned my daughter and she wasn't able to speak because of her emotions. My son's voice would suddenly halt. Those are the things that hurt. Much more than the surgery or the chemo. Seeing what happens emotionally to the members of your family is the most important side effect of cancer."

"We have had incredible support from friends and neighbours," says Stefan. "A lot of hospital visits, friends and neighbours who offer to do all possible and impossible favours. From groceries to gardening. My wife doesn't drive herself. The neighbours spontaneously organised a roster to take her to the hospital and pick her up again. Hats off to them all."

"The neighbours spontaneously organised a roster to take my wife to the hospital and pick her up again. Hats off to them for that!"

"From my professional experience, working in the pharmaceutical industry, I know that Belgium scores very well in terms of cancer survival. For example, the 5-year survival for colorectal cancer is 67.7%. That is a huge step forward compared to 10 or 20 years ago. We do not say enough about what we've already achieved. Especially in Western Europe, we are doing well with health care that is both of high quality and accessible. A great many people are still alive here who would have died a long time ago if they'd lived elsewhere - even in the US."



"There are more than 2,000 drugs for cancer in development. That is enormous. Pharmaceutical companies spend a quarter of their research efforts on cancer. In Europe, pharmaceutical companies invest more than 7 billion Euro in it. But we also have to be realistic: by far the majority of those 2,000 drugs in development will not lead to a breakthrough. Some, however, will. A number of targeted therapies and the current immune therapies really do make the difference for certain patient groups."

"Especially in Western Europe, we are doing well. We have health care that is both high quality and accessible. A great many cancer patients are still alive here who would have died a long time ago if they'd lived elsewhere - even in the US."

Getting started again with his former employer was difficult for Stefan Gijssels: "During my absence, the head office in the US imposed a major reorganisation with serious implications for my team. I couldn't live with all that strategic turnabout. So, on the first day that the doctors let me get back to work, I cleared my desk. Not long after that, I started my own company. I now work as an independent consultant. A fascinating new world was opened!"



5 Diagnosis, population screening and vaccination

Diagnosis

Scan and biopsy

Cancer can cause a multitude of symptoms, but sometimes none at all. Especially in the initial phase, many patients hardly experience any pain or inconvenience. This is why patients sometimes already have metastases at the time of diagnosis. Cancer symptoms depend on the nature of the tumour, its location, the rate at which it grows, the surrounding tissues that it affects, and so on.

A cancer diagnosis is a multi-stage process. After a thorough clinical examination, the doctor will do a blood test and/or refer the patient to a radiology department for imaging. There are different types of medical imaging in cancer medicine: ultrasound, traditional X-ray, radioisotope scans,

CT scan, NMR scan, etc. For some tumours the doctor can make a visual inspection (skin tumours) or use an endoscope (e.g. stomach, lung, bladder, uterine and intestinal tumours). In recent decades, much better detection methods have been developed in medical imaging to show tumours, but 'the gold standard' of the cancer diagnosis is still the microscopic examination of a biopsy - a piece of tissue from the tumour. This examination, carried out by a pathologist, usually, but not always, answers the question of whether there are cancer cells present, what type they are and at what stage they are in (see 'The eye of the pathologist').

THE EYE OF THE PATHOLOGIST

Classification of cancer types

Because there are different types of cancer, it is useful to catalogue and order them. Cancer is often classified according to the organ in which it originated. We then speak of breast, lung, skin or liver cancer. This is primarily an 'approachable' or 'comprehensible' classification, but this is not sufficiently useful for research and treatment.

That is why tumour types are classified by the pathologist on the basis of the cell type from which the tumour originated. That immediately leads to two major categories of tumours:

- **Carcinomas:** are tumours that develop from epithelial cells. These include skin cells, but epithelial cells also cover the mucous membranes on the inside of the lungs, intestine, mouth, oesophagus and so on. These are then classified further as adenocarcinoma (e.g. colon cancer, but also pancreatic cancer), squamous cell carcinoma (e.g. lung cancer and some forms of oesophageal cancer), etc.
- **Sarcomas:** are tumours that develop from supportive tissue such as bone, muscle, blood vessels, cartilage, fat, etc. Examples include osteosarcoma (bone tumour) and liposarcoma (a tumour that grows from fat tissue). Sarcomas are rarer than carcinomas. Carcinomas and sarcomas are called 'solid' tumours. This is in contrast to the 'fluid' tumours. These tumours originate from the progenitor cells of white blood cells and are found in the blood. Leukaemia and lymphomas are examples of these.

Tumour stage

For most cancers, four stages can be distinguished:

- *Stage I: Means that the tumour is still exactly where it originated. It has not yet grown into the surrounding tissues. Stage I is the initial stage.*
- *Stage II: The cancer has grown in the surrounding tissue but remains very close to the primary tumour. There are usually no cells in the lymph nodes or other organs.*
- *Stage III: Cancer cells have spread in the lymph nodes that drain the environment of the original tumour.*
- *Stage IV: The tumour has also spread in the rest of the body. Tumours in stage IV are also called advanced tumours.*

Molecular diagnostics

But even the pathologist does not always succeed in giving a conclusive answer or characterising a tumour (biopsy) in all its details. That is why more and more emphasis is placed on molecular diagnostics, in which laboratory research (for example, by genetic centres or clinical biology laboratories) looks for specific changes in the DNA of the tumour or test for proteins or biomolecules that are specific to certain tumours. (see 'Existing molecular tests and tests under development', p. 37).

One of the most advanced ways to characterize a tumour is to map the entire DNA profile of the tumour, or at least a large part of it. This is possible today by means of 'next generation sequencing', which uses sophisticated devices to read the genome of the tumour from end to end. This gives us insight into the range of DNA changes that control the tumour.^{25 26 27 28}

However, analyses like this - even though they are very profound - also have their limitations: the biopsy only provides a snapshot of the molecular profile of the tumour. A few months later, the

tumour may have developed considerably and already have a profile that is more in line with an advanced tumour. Moreover, a biopsy is only a representation of a part of the tumour, never of its complete composition. There is a chance that we will miss the profile of some subpopulations in the tumour. And, finally, it is not always possible to take a biopsy of the tumour.²⁹

From blood tests to liquid biopsy and cancer chip

For this reason, intensive research is being conducted into laboratory tests that can detect and/or characterise cancer in a blood sample. Some of these tests are not new and have been around for years, others are in the laboratory test phase or undergoing clinical validation (see 'Existing molecular tests and tests under development', p. 37).

The Holy Grail for every researcher who focuses on cancer diagnostics is the 'liquid biopsy'. In the liquid biopsy it would be possible to determine with certainty, from a small blood sample, whether someone has cancer and which form of cancer

it is, preferably at the earliest possible stage and with information about where the tumour is located. The idea behind liquid biopsies is that biological material from solid tumours - either proteins, DNA fragments or metabolic breakdown products - end up in the patient's blood and can be detected in it.³⁰

In January 2018, an American research group published the results of an experimental blood test called CancerSEEK for the early detection of various types of cancer.³¹ The test looks in the patient's blood for abnormalities in DNA fragments originating from tumour cells located elsewhere in the body (e.g. a colon tumour, lung tumour, breast tumour, etc.). What makes this test so distinctive is that the search for DNA abnormalities - in 16 genes - is combined with a panel of eight specific cancer proteins. The test was performed on 1,005 cancer patients with various cancers and on a large group of people who did not have cancer. In 70% of the cases, the test detected cancer and indicated the nature and location of the tumour. The ultimate goal is to further refine such analyses so that cancer can be detected at an early stage - even before visible symptoms appear - by means of a low invasiveness blood sample. Many validation steps are still needed before such a test becomes available for patients. But the fact that the 'proof of concept' has now been delivered is a big step forward in the early detection of cancer.

Molecular diagnostics, however, do not have to be limited to DNA abnormalities and proteins. There are researchers who are now trying hard to detect cancer by testing for metabolites. This is because tumour cells have a different metabolism from normal cells. Traces of these metabolic products can be found elsewhere in the body - not only in blood, but also in urine, saliva or faeces.³²

There are also developments in electronics and nanotechnology for helping to diagnose cancer. A number of research institutes are working on chips that detect cells, proteins, DNA, RNA and/or other molecules from cancer cells in a drop of blood. The test data is collected, processed and passed on in a few minutes as structured results to the doctor's computer or smartphone.³³

These are all hopeful diagnostic developments, and we are still only at the start of a tidal wave of such new technologies.

Population screening

The earlier a diagnosis is made in the cancer's development, the sooner treatment can be started and the higher the chances of survival and healing. For this reason, the Flemish government organises and finances three population screenings for the early detection of cancer: colon, cervical and breast cancer.³⁴

It is noticeable that only slightly more than half of the target group actually participates in the three screening programs. That figure should be much higher. There are, after all, major benefits to detecting cancer at an early stage. Although there may also be disadvantages attached to the population screening for some patients. To decide whether or not you want to participate it is important that you get good advice from your doctor or via one of the websites listed on page 38. On these websites you will find neutral information about what the research entails, what its purpose is and what you can expect from it.

EXISTING MOLECULAR TESTS AND TESTS UNDER DEVELOPMENT

Some existing tests

- *The PSA test that measures the 'prostate specific antigen' in the blood is still the most common test for detecting and monitoring prostate cancer.*
- *Other markers are mainly used for follow-up during and after cancer treatment. Examples of these include the 'cancer antigen 15.3' (CA 15.3) for the follow-up of breast cancer, CA 125 for ovarian cancer, NSE for lung cancer and AFP for testicular cancer and liver cancer.*

A selection of molecular tests under development:

- *The MammaPrint is a genetic test for examining breast cancer tissue. The test gives an indication of the nature and aggressiveness of the tumour. With an aggressive tumour there is a greater chance of recurrence and preventive chemotherapy is therefore recommended. The MammaPrint makes it easier to judge whether a patient will benefit from chemotherapy.^a*
- *Some sugar variants in the serum can be used as biomarkers to predict which patients with liver cirrhosis are at increased risk of liver cancer (GlycoCirrhoTest).^b*
- *The immune system switches on certain immune cells to clear up tumours. One example of immune cells that are activated by nascent intestinal tumours are peripheral monocytes. The Colonokit measures, based on a set of 23 monocyte-specific genes, whether someone has colon cancer at an early stage.^c*

Finally, though, you decide yourself whether to participate. But make that decision consciously and on the basis of good information!

"Why isn't there a screening program for prostate cancer?" Is a question that is often asked. Prostate cancer is, after all, the most common cancer in men. The answer is straightforward: preventive screening of the population is only useful if there is a test that is reliable, simple, affordable,

acceptable and sufficiently comfortable for the patient. A cancer screening test must be able to detect cancer with great certainty at an early stage - or, even better, at a precursor stage - and there needs to be a treatment with a high success rate for that specific cancer type. The reliability of the most common test for prostate cancer - the PSA test - is insufficient for it to be rolled out in a population screening program.

THREE POPULATION SCREENINGS FOR CANCER

Colorectal cancer - The Flemish screening program for colorectal cancer gives men and women aged 55 to 74 the chance to take a bowel test every two years. This test looks for traces of blood in the faeces. This can point to colon cancer or intestinal polyps, which are the precursors of colon cancer. If an abnormality is found, a colonoscopy, which is a visual inspection of the inside of the large intestine, is proposed.

Of every 1,000 participants, 50 were referred for additional colonoscopy (2015 figures). For 15 of these 50 patients nothing was found and for 30 patients intestinal polyps were detected and removed. Five patients were referred for a colon cancer treatment.

For more information on this, go to: dikkedarmkanker.bevolkingsonderzoek.be/en

Cervical cancer - The population screening for cervical cancer urges all women aged 25 to 64 to take a cervical smear every three years. This smear is then examined in the laboratory for the presence of abnormal cells. Cervical cancer develops very slowly. Cells often show detectable abnormalities even before they become cancer cells. This is a preliminary stage that either does not need to be treated or only by a relatively simple procedure (<1%).

For more information, go to: baarmoederhalskanker.bevolkingsonderzoek.be/en

Breast cancer - The Flemish government started the breast cancer screening program back in June 2001. The screening program is intended for women aged between 50 and 69. Every two years they are offered a mammographic examination.

Of every 1,000 women who were screened in 2015, 975 were told that there were no abnormalities. Additional tests were needed for 25 women, after which breast cancer was diagnosed in 5 of them.

For more information, go to: borstkanker.bevolkingsonderzoek.be/en

Preventive cancer vaccination

In addition to early detection via screening, preventive vaccination is also possible for some cancer types.

Cervical cancer

More than 150 subtypes of the human papillomavirus (HPV) exist. Some of these can cause cervical cancer in women. HPV is mainly transmitted through sexual contact. Research shows that a large proportion of the sexually active women are infected with HPV. Three vaccines against HPV have been registered in Belgium. Since 2010, HPV vaccines have been part of the basic vaccination scheme for children and adolescents. Girls get the vaccine for free before they are sexually active via the CLB (Centres for Student Guidance) in the first year of secondary education. Alternatively, girls can be vaccinated by their GP or gynaecologist. In some countries

boys are also vaccinated against HPV. They too can be carriers of HPV and pass it on to girlfriends through sexual contact.

Liver cancer due to hepatitis B

People with a chronic form of liver inflammation as a result of infection with the hepatitis B virus have an increased risk of liver cancer. It is estimated that 150 people in Belgium get liver cancer every year as a result of chronic hepatitis B. Vaccination against this virus is included in the basic vaccination programme and is currently administered to babies at the age of 8, 12 and 16 weeks and repeated at 15 months. Although the hepatitis B vaccine is mainly administered to prevent a liver infection with this virus, a side effect is undoubtedly that in the long term the number of victims of liver cancer as a result of chronic hepatitis B infection will fall.

Dirk Veldeman

"When it comes to population screenings for colorectal cancer, cervical cancer and breast cancer, Dirk argues from a sense of social solidarity: "Thanks to these screenings, society can save a lot of money and prevent unnecessary suffering. Those who are early enough can usually be helped with less invasive treatments. This is not only good for the patient, but also for the health care budget. But too few people take part in the population screenings. We really need to look for communication and awareness-raising strategies that convince target groups to participate. It should be popular and matter-of-course. Just as natural as taking the car for an MOT test every year."



6 Cancer therapy

Conventional therapy is still the treatment for most cancer patients.

For the vast majority of cancer patients, surgery, radiation and/or chemotherapy still form the basis of their treatment. Surgery has the great advantage that the surgeon can do a root-and-branch removal of the tumour in a number of cases (for example in breast cancer). In radiotherapy, a beam of ionizing radiation is directed at the location of the tumour. The radiation kills the cancer cells or slows down their growth by extensively damaging the tumour DNA.

Chemotherapy is a treatment with drugs that have an inhibitory (cytostatic) or killing (cytotoxic) effect on rapidly dividing cancer cells. These drugs, however, make little distinction between dividing cancer cells and dividing healthy cells. As a result, the bone marrow, the mouth, the intestines, skin and hair follicles are sometimes hit hard by chemotherapy with the well-known side effects such as hair loss and digestive problems.

But there are also new developments in these 'conventional' treatments. Surgeons, for example, are experimenting with devices that tell them during the operation whether they are cutting into tumour tissue or healthy tissue,³⁵ while proton therapy is a recent radiation technology in which tumours are destroyed more accurately by irradiation with small particles.³⁶ With this technology, the damage to tissues surrounding the tumour is greatly reduced leading to fewer side effects.

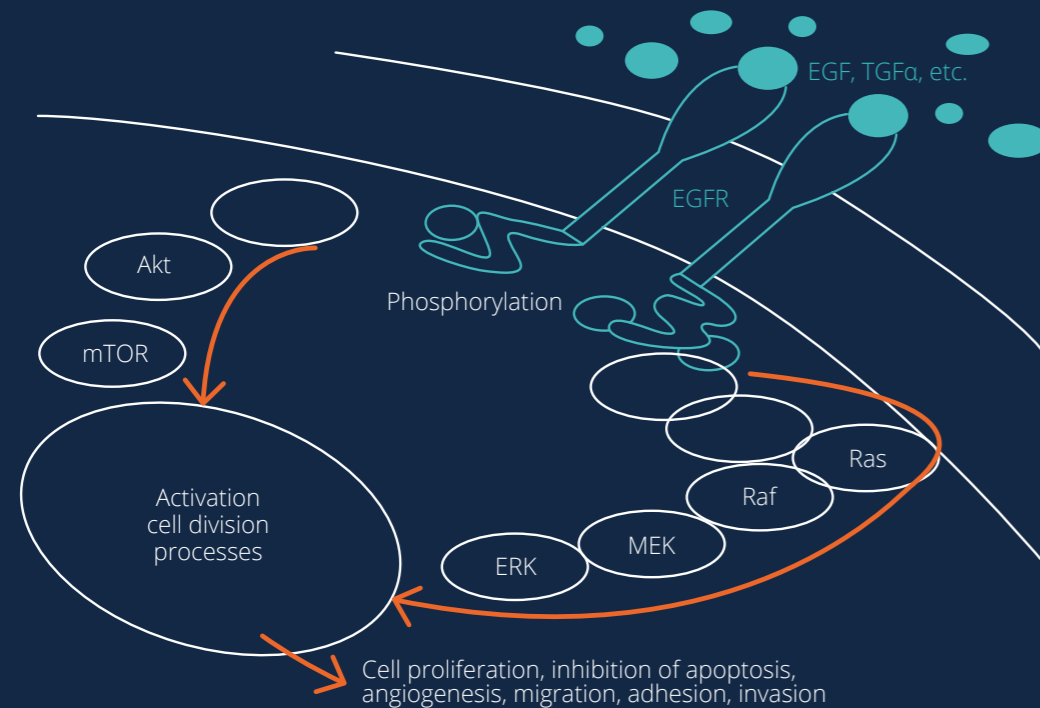
A form of cancer that is never treated surgically is leukaemia, also known as blood cancer. Although the treatment of leukaemia with the new drugs (see the following sections) has improved spectacularly, it is sometimes still necessary to proceed to a bone marrow transplant with stem cells from the patient or from a donor. Stem cell transplants are also increasingly used in patients with solid tumours if they undergo intensive pre-treatment with chemotherapy or radiation. Such heavy pre-treatments can severely weaken patients and their immune system.

Targeted medicines

Thanks to the basic research on cancer cells (see Section 4) we have not only gained insight into the biological signal chains that control cancer, we have also used this knowledge to design new medicines. These are drugs that specifically target the modified biological reaction chains in cancer cells. This is why these drugs are also called 'precision' or 'targeted' medicines or personalized medicines tailored to the patient, in contrast to traditional 'one size fits all' chemotherapy drugs. The best known examples of such drugs are trastuzumab (Herceptin) against a specific form of breast cancer, imatinib (Glivec, Gleevec) against specific forms of leukaemia and GIST tumours, cetuximab (Erbix) against some intestinal cancers etc. (see 'The biology behind precision medicines', p. 42).

THE BIOLOGY BEHIND PRECISION MEDICINES - SOME EXAMPLES

- **Cetuximab** (Erbix) is an antibody that inhibits the action of the EGFR (epidermal growth factor receptor). It is used to treat specific forms of metastatic colon cancer and head and neck cancer. EGFR is a protein that crosses the cell membrane (see illustration). On the outside, it has 'antennas' for binding signalling molecules such as EGF and transforming growth factor- α (TGF α). After EGF or TGF α binding, EGFR will activate a series of proteins on the inside of the cell - including the Ras-Raf-MEK-ERK chain and the Akt-mTOR chain - which in turn will stimulate the cell to divide.⁹ Cetuximab ensures that EGFR can no longer be activated by EGF or TGF. The tumour division of colon cancer cells depends on the interaction between EGFR and the signalling molecule Ras, which is part of the aforementioned chain. However, if a mutation has occurred in Ras, the cell will continue to divide, independently of the interaction between EGFR and Ras. Blocking this interaction with Cetuximab is then useless.



- **Trastuzumab** (Herceptin) is an antibody that inhibits the action of ERBB2 (also called Her2/Neu). ERBB2 also belongs to the family of receptors for EGF. The ERBB2 receptor occurs in much higher concentrations in 15% to 30% of all breast tumours. Trastuzumab disables ERBB2. By giving patients with this type of breast cancer chemotherapy combined with trastuzumab the mortality risk falls by 20% and the average survival increases by five months.⁹
- **Imatinib** (Gleevec or Glivec) inhibits the fusion protein BCR-ABL1. ABL1 is what is known as a tyrosine kinase: it activates various other proteins by attaching phosphate groups to them. By fusing with BCR, ABL1 becomes permanently active. It therefore has a disruptive effect on many cellular processes, including cell differentiation, cell adhesion, stress response and cell division. Imatinib is used against chronic myeloid

leukaemia (CML) and some other forms of leukaemia, but is also successful against gastrointestinal stromal tumours (GIST).^{c,d}

- **Olaparib** (Lynparza) inhibits the poly ADP-ribose polymerase (PARP). PARP belongs to a family of proteins that repair single-stranded DNA breaks. In combination with DNA-damaging platinum compounds, PARP inhibitors cause so much DNA damage that apoptosis of the tumour cells occurs. Olaparib is successful against tumours of the ovaries caused by BRCA mutations.^e

'Personalised medicine'

The other side of the coin is that not every patient is eligible for targeted therapies. As a result, therapy with a targeted drug is usually preceded by a biomarker test - often a DNA test - that checks whether the profile of the tumour fits the requirements of the precision medicine. Examples of such include the Ras test for colorectal cancer or the Her2/Neu assay in breast cancer (see 'The biology behind precision medicines').

Some researchers and doctors use the term 'personalised medicine' for such biomarker-guided therapy. In fact, it is a form of medicine that divides patients into subgroups: those who will benefit from a particular drug, and other who don't. The appropriate treatment is only chosen after the test. This approach is more efficient and less valuable time is lost than when you have to find the right treatment by trial-and-error.

Building-up resistance

Nevertheless, targeted medicines also have their limitations. It soon became clear that many tumours manage to build up resistance to them, just as they do with chemotherapy, by the accumulation of additional mutations and the development of resistant subpopulations of tumour cells. It is an evolutionary process in which the therapy puts selective pressure on the tumour and the tumour

cells use escape routes to evade this pressure. This resistance can occur some months after the start of treatment in some patients, but can take years to develop in others. Targeted medicines are therefore rarely given as monotherapy, but rather in combination with classical therapies or even in combinations with other precision medicines (see the section 'The future of therapeutic cancer research', p.54).

Angiogenesis inhibitors

Signal molecules such as VEGF (vascular endothelial growth factor) cause existing blood vessels to branch and form new blood vessels. This process is called angiogenesis. Cancer cells also release VEGF and other signal substances to activate nearby blood vessels. The blood vessels form side branches and grow towards and into the tumour. Without those blood vessels, the tumour cells become starved of oxygen and nutrients.

In recent decades various drugs were been developed that block VEGF or the underlying signal chains. The best known angiogenesis inhibitor is undoubtedly bevacizumab (Avastin), an antibody that hinders the action of VEGF by binding to it.³⁷ ³⁸ Angiogenesis inhibitors were originally developed to 'starve' primary and metastatic tumours by blocking the growth of blood vessels.

But things turned out to be a bit more complicated than that. Avastin - just like other targeted therapies – does not work in the same way in cancers of different organs and usually has only a limited effect in monotherapy: it does not always significantly prolong patient survival, despite the observation that tumour growth is indeed slowed down.^{39 40} Avastin is therefore usually given in com-

bination with other anti-cancer medicines. Additional research shows that other signaling agents that respond to blood vessel formation also have potential as anticancer drugs. It has also been shown that the mechanism behind the action of angiogenesis inhibitors may be very different from what was assumed until recently (see infobox 'Leaking vessels ... the Achilles' heel of tumours').

LEAKING VESSELS ... THE ACHILLES' HEEL OF TUMOURS

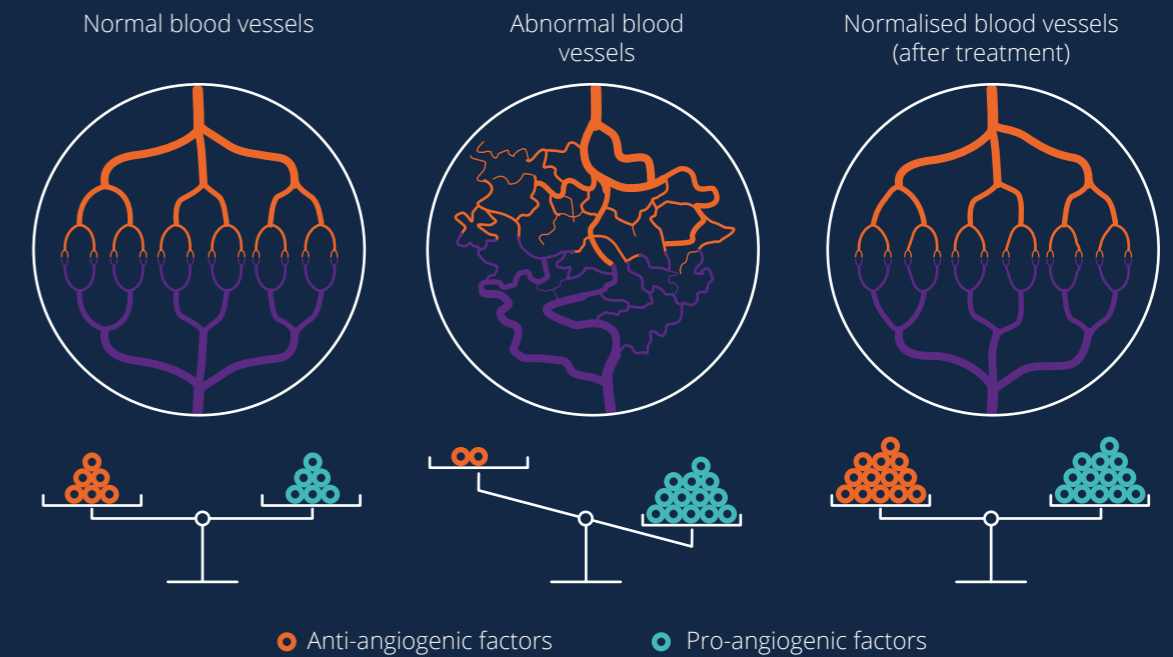
Anti-PIGF as an alternative to anti-VEGF

VEGF and its sister molecule PIGF (placental growth factor) play a critical role in the growth of blood vessels in a tumour. They ensure that blood vessels grow towards the tumour cells to supply them with oxygen and nutrients. However, existing VEGF inhibitors also block blood vessel formation in healthy tissue. For example, they cannot be given to pregnant women because they endanger the development of the foetus. Moreover, tumour cells also rapidly build resistance to VEGF inhibitors. There is therefore a need for other anti-angiogenic targets. PIGF seems to be a valuable alternative. PIGF only stimulates blood vessel formation in cancer and other diseases and, unlike VEGF, is not very important in normal developmental processes. Anti-PIGF inhibits angiogenesis in cancer tissue, appears to induce less resistance and has no effect on normal blood vessel growth in healthy tissue. It is therefore a promising candidate for further testing as a new drug for certain types of cancer such as medulloblastoma, which is a brain tumour that occurs in children.^{a b}

Towards a new treatment concept: normalizing blood vessels

Researchers have found that newly formed blood vessels in tumours are both structurally and functionally abnormal. Due to an excess of pro-angiogenic factors (including VEGF) and a shortage of anti-angiogenic factors, blood vessels in tumours grow too quickly and do not mature adequately. The result is that they leak, grow out in all directions and do not make the right connections. This creates a hostile microenvironment in the tumour characterised by a shortage of oxygen and nutrients, high acidity and a greatly increased physical pressure. These conditions feed tumour progression and increase the tendency to metastasis (spreading).^c

This led cancer researchers to suspect that VEGF inhibitors actually act by restoring the balance between pro- and anti-angiogenic factors rather than by 'starving' tumours. VEGF inhibitors can cause tumour blood vessels to develop more 'normally', reducing the oxygen deprivation and fluid pressure and thereby the tendency of cancer cells to spread. This opens up an alternative therapeutic window: because of the normalization of the blood vessels, medicines can penetrate the tumour much more efficiently and easily. This let them perform their tumour-killing task more effectively.^d



The metabolic perspective of blood vessel cells

More recently, it has become clear that intervening in the metabolism of blood vessel cells (endothelial cells) might offer a new and promising therapeutic strategy against cancer. Endothelial cells, the cells lining the inside of the blood vessel wall, support angiogenesis. Research has shown that the breakdown of sugars (glycolysis), oxidation of fatty acids and glutamine metabolism are important regulators for blood vessel formation in cancer. For example, normal blood vessel cells need sugar to be able to produce enough energy to form new blood vessels. Blood vessels in tumours grow rapidly. For this, the blood vessel cells need large amounts of sugar and their metabolism gets 'overheated'. This overheating might possibly be slowed down by blocking the sugar metabolism so that the blood vessel cells go back to 'normal speed' and function better. There may be unexplored therapeutic opportunities here.^{e f g h}

Those other vessels ... lymph vessels

Cancer cells need roads to spread, to metastasise. In addition to blood vessels, cancer cells make extensive use of lymph vessels, which drain the tissues around the tumour, to metastasise. However, cancer can also create new lymph vessels. Until now scientists knew little about the factors that regulate the growth of new lymph vessels. This is slowly changing. Recent research shows that lymphatic vessels are fond of specific fats - but not the fats that we find in our traditional diet. Intervening in the availability of these very specific fats might possibly control the growth of new lymphatic vessels ... and thus also the metastatic capacity of tumours.ⁱ

Immunotherapy

The newest addition to innovative cancer treatments is immunotherapy. Immunotherapy is not new in itself. Decades ago doctors used mixtures of bacteria to strengthen the immune system of cancer patients - but success was by no means guaranteed. Yet it is a concept that is still used today: weakened tuberculosis bacilli are still used as a treatment for bladder cancer. Nowadays, there are various forms of 'modern' immunotherapy, but the common characteristic is the strengthening or stimulation of the body's own defence mechanisms to clear up cancer. Below we discuss three forms of immunotherapy, namely immune checkpoint blockers, CAR T-cells and dendritic vaccination, but there are several other variants under development. Some immunotherapies are already in use, while others are still in the research phase.

Immune checkpoint blockers

Researchers found that immune cells are physically present in most tumours. But those cells are, in one way or another, not active. It is as if the cancer cells have lulled them to sleep. All this has to do with what are called immune checkpoints (see 'The biology behind immune checkpoint blockers').

Spectacular but nuanced

The first publications on the use of immune checkpoint blockers were spectacular. In some patients with metastatic skin cancer (melanoma) or metastatic lung tumours, the use of checkpoint blockers led to almost complete recovery. Normally these people would have had only a few months to live!

Today, checkpoint blockers are used against melanoma, non-small cell lung cancer, kidney and bladder cancer, head and neck tumours and Hodgkin lymphoma. The results are still promising, but not for all patients. For example, of the 1,861 patients

with metastatic melanoma treated with a CTLA-4 antibody, "only" 22% were still alive after three years. However, the prospects for this group of 'survivors' were particularly good.⁴¹

A similar effect was seen in lung cancer patients who received a checkpoint blocker after other treatment options had failed. After five years, survival was 16%. Without this immune checkpoint blocker, the 5-year survival in this group was estimated at a mere 4 to 5%.⁴²

Conclusion: there is indeed a group of patients who live much longer thanks to this new therapy, even though they had previously been declared 'untreatable' because their cancers had progressed too far. Why does immune therapy work in some of these patients and not in others? Can we also pre-select the eligible patients for these treatments via a biomarker profile, as we do with precision medicines? The research is in full swing.

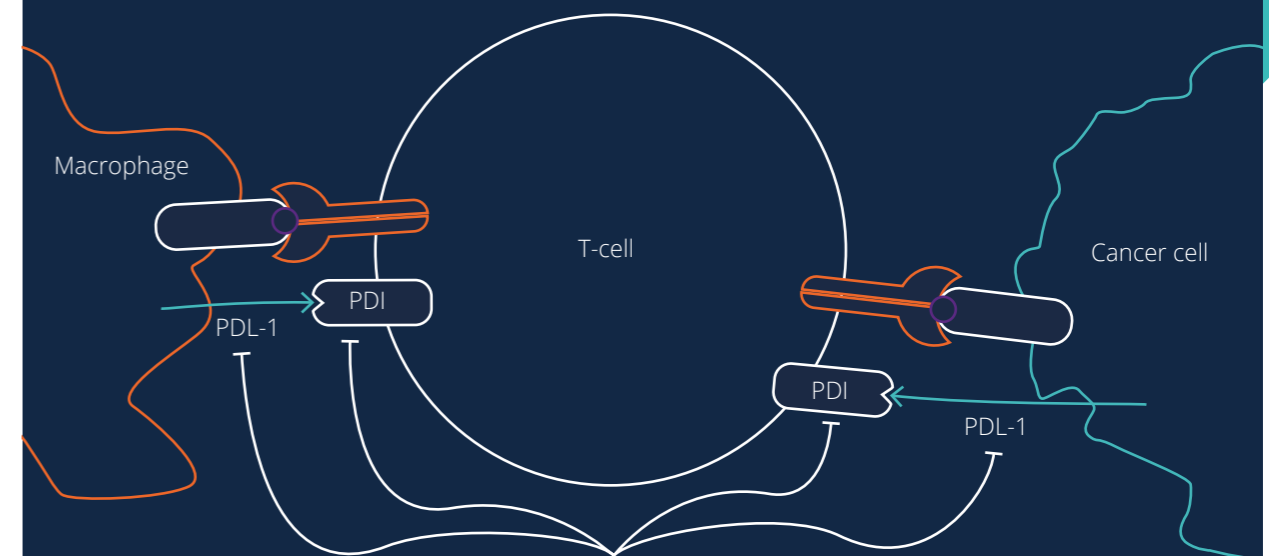
In addition, researchers expect that they can boost the effectiveness of immune checkpoint blockers by administering them in combination with other (precision) medicines. It is estimated that there are currently no fewer than 1000 clinical cancer studies aimed at increasing the effectiveness of checkpoint blockers in larger groups of patients.^{43 44}

Dendritic cell vaccination

In a completely different strategy, researchers are trying to activate T-cells against cancer cells via a vaccination strategy. Cancer cells have molecules on their cell surface - foreign antigens - that distinguish them from the other body cells. A normally functioning immune system recognises these antigens and tries to destroy the cancer cells. With tumour vaccines, this natural ability of the immune system is stimulated and even strengthened (see 'The biology behind dendritic cell vaccination').⁴⁵

THE BIOLOGY BEHIND PD-1, PDL-1 AND CTLA-4 IMMUNE CHECKPOINT BLOCKERS

The human body uses checkpoints to prevent the immune system from massively attacking its own body cells. An example of such a checkpoint is PD-1, a protein found on the outside of T-cells (see figure). PD-1 is a receptor for PDL-1 ('PD-Ligand-1'). If there is a bond between the two, the T-cell defence activity is stopped, as if a brake pedal had been pressed. Just about every cancer cell produces PDL-1. That is why T-cells and cancer cells can often live side by side. CTLA-4 is a similar immune checkpoint, and more and more of these checkpoints are being discovered.



Nivolumab (anti-PD-1), Pembrolizumab (anti-PD-1), Atezolizumab (anti-PDL-1)

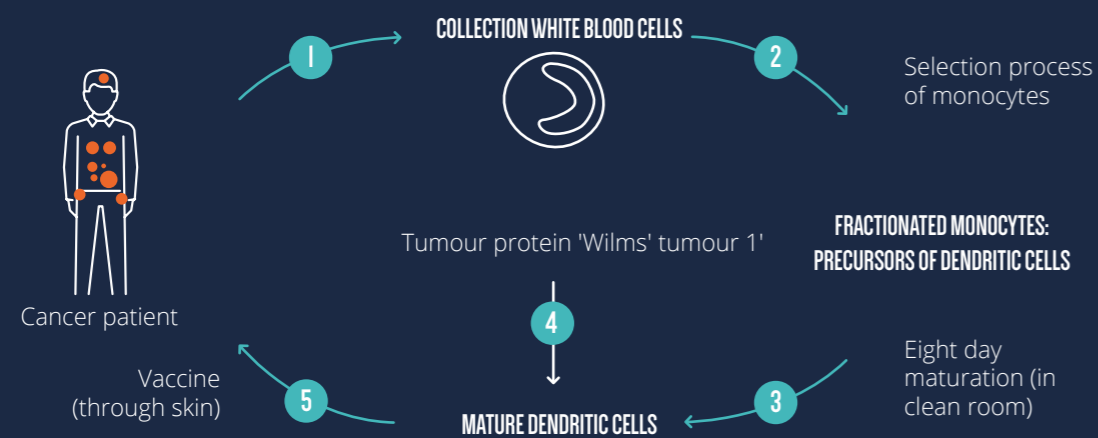
To counter the neutralisation of T-cells, researchers developed antibodies against, for example, PD-1, PDL-1 and CTLA-4. These include the PD-1 blockers nivolumab (Opdivo) and pembrolizumab (Keytruda), the PDL-1 blocker atezolizumab (Tecentriq) and the CTLA-4 blockers ipilimumab (Yervoy) and tremelimumab. These antibodies ensure that cancer cells can no longer slam the brakes on to protect themselves against the immune system. As a result, the immune system again recognises the cancer cells and can destroy them.⁹

THE BIOLOGY BEHIND DENDRITIC CELL VACCINATION

One form of immunotherapy currently being actively investigated is dendritic cell vaccination. Dendritic cells belong to the white blood cells and act as the 'antennas' of the immune system. They constantly monitor the body for the presence of foreign substances and cancer cells. They have the ability to 'eat' these foreign substances and present fragments of these substances on the outside of their cell membrane to T-cells, including T-killer cells. This activates the T-cells against the tumour, which they try to destroy.

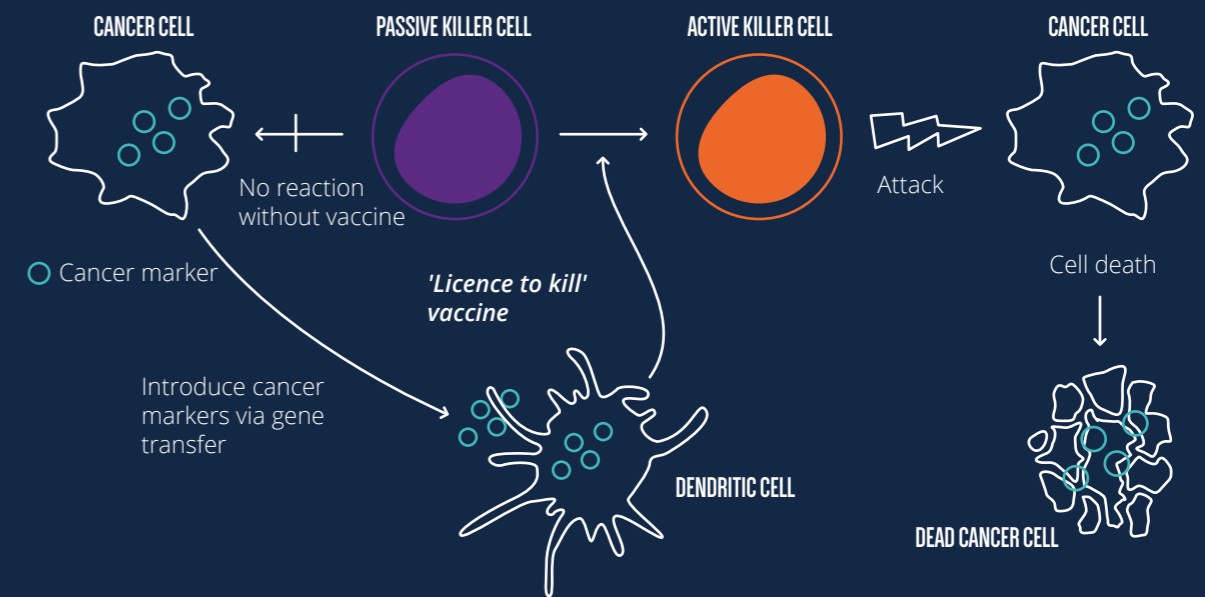
It are these 'antigen presenting cells' that are used in dendritic cell vaccination. The procedure is as follows: Monocytes - a type of white blood cell - are isolated from the blood of the cancer patient and differentiated into dendritic cells in the laboratory. These dendritic cells are loaded with a protein that is produced specifically by the tumour cells. In this example, it is the Wilms tumour 1 protein (WT1). The dendritic cells, which now present parts of the WT1 protein on their outside, are reintroduced into the patient. (Drawing 1)

Once inside the patient, the dendritic cells will present WT1 to T-killer cells, which are thereby activated against the tumour cells carrying the same WT1 label. (Drawing 2)



Drawing 1. Source: Dr. Sébastien Anguille, Prof. Viggo Van Tendeloo & Prof. Zwi Berneman, Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Belgium.

Dendritic cell vaccination or DC-Vac is a treatment that is truly tailored to the patient. It is, after all, the patient's own body cells that are isolated, cultivated and manipulated in the laboratory and then injected back into the body to activate killer cells that can clean up cancer cells. DC-Vacs have been and are being tested in clinical studies against brain tumours, leukaemia and bladder, skin, kidney, breast, cervical and prostate cancer.^{a, b, c, d, e} In the United States, one drug is currently registered on the basis of cell vaccination, namely sipuleucel-T (Provenge) for the treatment of metastatic prostate cancer.^f



Drawing 2. Source: Dr. Sébastien Anguille, Prof. Viggo Van Tendeloo & Prof. Zwi Berneman, Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Belgium.

CAR T-cells

Similar to dendritic cell vaccination, but with a different 'flavour', are CAR T-cells. This method also collects white blood cells from the patient – in this case T-cells. These cells have then the gene for a 'chimeric antigen receptor' (CAR) implanted using a weakened virus. These CARs are artificially constructed receptor proteins that recognise specific molecules on the outside of cancer cells. Once the genetically modified T-cells are reintroduced into the patient, they will multiply further. In addition, guided by their newly-designed receptor, they will recognize cancer cells and initiate a mechanism to kill them.⁴⁶

At present, several clinical studies with CAR T-cells are being performed around the world. In 2017, the American Food and Drug Administration (FDA) approved the first two CAR T-immunotherapies. In both cases, the T-cells were implanted with a receptor against the B-cell antigen CD19. These therapies were directed against specific forms of leukaemia. The FDA approval is undoubtedly an important step forward in the development of CAR T-therapy for the treatment of cancer.



The story of

FLO DE GEYNDT

"I'm living now", says Flo De Geyndt, 24 years old, the youngest of three, "but I didn't really have a childhood. From the age of nine many things started to change: on a weekday evening I had my first epileptic seizure. In the weeks and months afterwards I occasionally had absences. I was absent from the world for a moment and suddenly 'woke' again after a few seconds. During the summer holidays, these attacks happened more and more and lasted longer. In the hospital, doctors saw 'a ball' in my brain. At first I was given medication for a mild form of epilepsy. But after numerous investigations into 'that little ball', more than a year later, it was decided to remove it surgically."

"After the operation, the absences stopped. I still had to take the medication, but my parents were able to see my old cheerful self again. On the day I left the hospital, the doctor came to talk to me. She asked what I knew about cancer."

"I don't remember the rest of that conversation", says Flo, "but a few minutes later my parents came back into my room. My dad was clearly grief stricken. He was never like that. My immediate feeling as a 10 year old was that something was not right at all. I remember that they looked at me and smiled sweetly and that I reacted: yes, but I don't have cancer do I? And then it started." Flo

was given radiotherapy. 30 treatments. Every day after school. "I always wore hair bands before I was ill, so fortunately it was less noticeable that I had to wear one every day from then on. Because of the radiation, I mostly lost the hair on my right side. What's more, I felt so tired." That fatigue led to problems at school and it also cost the growing Flo a big part of her social life: going to birthday parties, staying with a friend, spending a full day shopping, ... it just wasn't possible. She was regularly the target of nasty comments. Classmates thought she was lucky: she could do a test later or she did not have to go to class. While going to class as a normal child was precisely what Flo wanted to do.

"There was also that endless search for guidance, help and care. Fortunately, I got huge support from my parents, brother and sister."

In 2007, a follow-up scan showed that the tumour had returned. A second operation followed, and a referral to an experimental form of immunotherapy ... in another hospital. White blood cells from Flo were taken and immunised against the tumour. She had to go to the hospital for injections every month.





But did this form of immunotherapy help? "I think so, but I'm not sure", says Flo. In any case, three years later, new tumour growth was detected. Another operation. This time there was no follow-up treatment. "I managed to graduate grammar school. But in 2011, when I'd only just started college studying photography, a scan showed that the tumour was back again. This time the doctors gave me a bad prognosis. They said I didn't have much longer to live. I had just turned 18. At first, I didn't want a new operation. I was afraid and still wanted to do so much, but I also knew that it didn't make sense to waste time by stressing. Planning a long journey was no longer possible. My mum took me to London for a few days. A positive attitude is very important, for the operation, but also enormously important for the recovery. Just before my fourth operation, I grabbed my parents once again and

said 'Let's do this shit!.' Flo came out of that fourth operation well. A few days later her doctors came with incredible, fabulous, extraordinary news: there were no more malignant cells present in the tumour. "I do not know if you can talk about a medical miracle, but even today no one can find an explanation for it." Flo started to live 'hard'. She had a lot to catch up on. A complete childhood ... until she fell into a deep pit. Eleven years of living with cancer without significant psychological counselling had taken its toll. Moreover, some important people had disappeared from her life. A jet-black period ... all the positives of being able to live further was countered by a mountain of unresolved feelings and traumas. Frustrations, because she couldn't recover her lost youth. And the limitations imposed by the weakened body that had already experienced so much. "There was also that endless search for

guidance, help and shelter. Fortunately, there was huge support from my parents, brother and sister."

**"Five years after my last brain operation,
I wrote a text and shared it on Facebook.
That day felt like a liberation. I'm living again."**

"Five years after my last brain operation, I wrote a text and shared it on Facebook. That day felt like a liberation. I'm living again. Two years ago I took part in the 1,000 kilometres cycle ride against cancer. Fortunately, I found a huge passion through everything: photography. This gives me a lot of energy in various ways. And, I just got my driving license. When I got that, I felt I'd come a step closer to

a 'normal' life. A life like others of my age, something I could finally do." Flo's life, however, goes on through trial and error, with ups and downs. Not always easy, and not for the people around her either - Flo is very much aware of that: "Last year there was another medical crisis and a benign tumour had to be removed from my lower back. But today I am full of ambitions again. I did the 1,000 kilometres again, for example. Although I hadn't really trained enough for it. Writing a book about the path I've gone down and my experiences is something I've really wanted to do for a long time. Maybe there's a chance that I could help or inspire people with that. Don't forget, they cut into my head four times when I was little and I was irradiated 30 times. That's something I carry with me."



7 The future of therapeutic cancer research

The half-full glass

Over the past thirty years, our knowledge of the molecular and cellular biology of cancer has increased spectacularly. This has led to a significant increase in new medicines (see previous sections in this dossier). In addition, pharmaceutical and biotech companies have many more new products in the pipeline.

That is good news for those who suffer from cancer, because some of the new medicines really make a difference. They manage to cure patients and stabilise others for a long time while maintaining quality of life: think, for example, of imatinib for chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST), trastuzumab for a number of women with breast cancer or the new immune checkpoint blockers for patients with melanoma or lung cancer.

Other medicines, however, don't live up to their promise. They often inhibit the growth of a tumour, but do not always lead to a significantly longer survival of the patient, let alone to a cure. That is why some people see the glass as half empty rather than half full: they emphasise that tangible progress for the cancer patient is frustratingly slow in coming. The bar for drug development needs to be raised. Much higher, in their view.⁴⁸

Clinical studies

Doctors and researchers around the world try to contribute to this. It is estimated that more than 1000 anti-cancer drugs are being tested in clinical trials.⁴⁹ A look at the website [ClinicalTrials.gov](https://www.clinicaltrials.gov) shows that almost 22,500 clinical cancer studies are currently registered as 'ongoing' or 'planned'. That is a record.

By participating in 875 ongoing or planned studies, Belgian hospitals and research institutions are particularly well represented. In concrete terms, it means that Belgium participates in 80 cancer studies per million inhabitants. In this respect we score 1.5 times better than the Netherlands, 2.5 times higher than France and the US, and 4.7 times better than Germany.

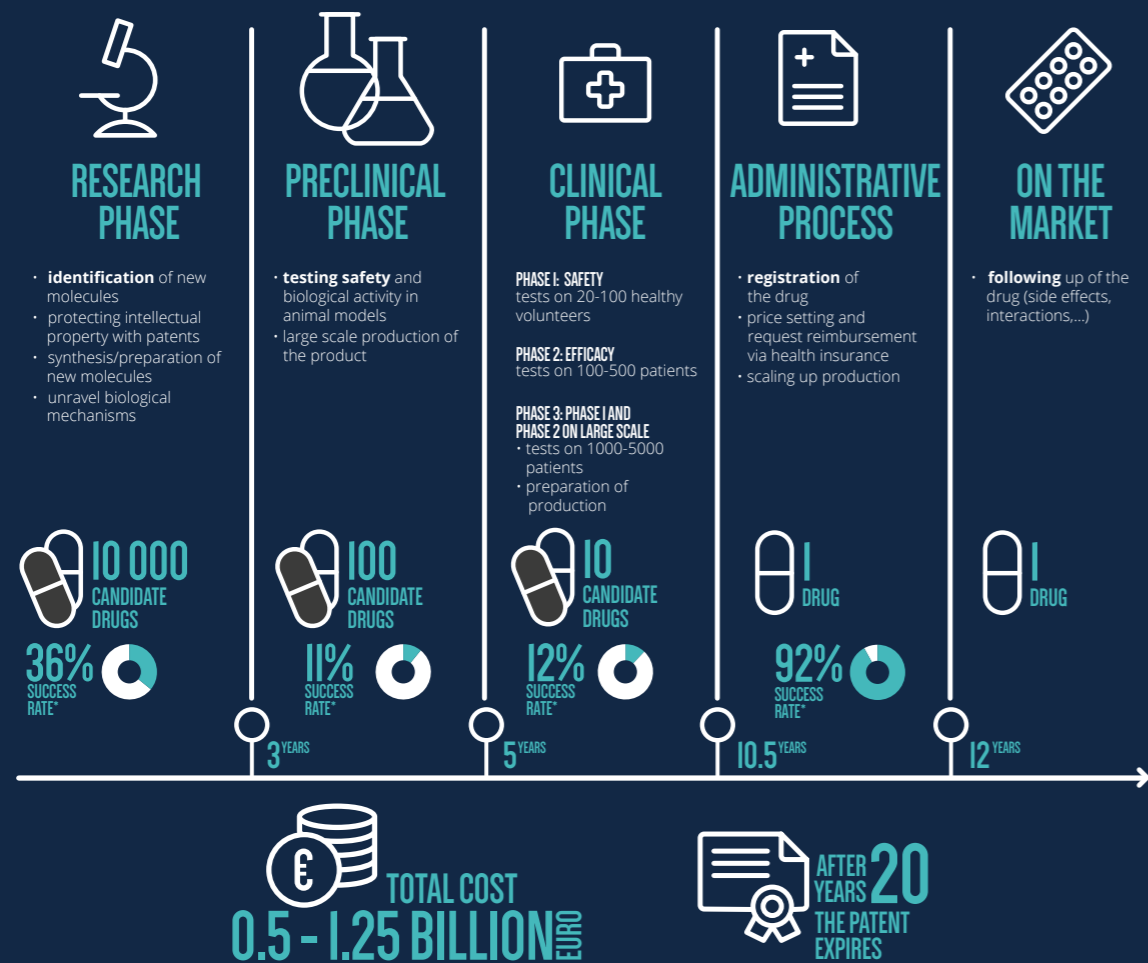
However, we must not forget that before a new medicine reaches the patient it has to undergo a time-consuming, complex, intensive and expensive process (see 'The development of a medicine', page 56). Clinical studies are part of this, but are preceded by a preclinical phase and followed by a registration phase.

Research into new cancer treatments has to deal with a series of specific challenges in not only the discovery phase, but also in the preclinical, clinical and approval phases. We have to look for creative solutions for all those challenges.

THE DEVELOPMENT OF A MEDICINE

The process for turning a molecule into an authorized medicinal product is long and complex. Before it comes on the market, each candidate drug is tested for safety and efficacy - does the medicine do what we expect and in a safe way? This evaluation first takes place in the laboratory and on experimental animals (preclinical phase), and then in clinical studies, which we generally subdivide into three to four phases:

- In a Phase I clinical study, the safety and effect of the drug is analysed on a small number of volunteers. Checks are made to see whether serious side effects occur.
- If everything turns out to be safe, a Phase II clinical trial begins in which a small group of patients is tested to see if the drug has an effect on treating the disease (e.g. slower tumour growth, less chance of metastases, longer survival or improved quality of life).
- If Phase II yields hopeful results, a Phase III clinical trial is performed in which the safety and efficacy of the drug is further investigated in a large group of patients. Only when these results are positive will a candidate drug be admitted to the market by the competent government authorities.
- In Phase IV, when the medicine is on the market, a larger group of patients is monitored to detect any undetected side effects over the long term.



* The success rate for proceeding to the next phase

It takes an average of 12.5 years to develop a drug in Europe and costs around 500 million to 1.25 billion Euro. Because of the development costs and the high risk that a medicine will disappoint in a certain phase, it is virtually impossible for government laboratories and research centres to complete this entire process on their own. That is why a medicine can almost never be developed without the capital and specific expertise of the biotech and/or pharmaceutical industry - not even for cancer medicines.

Challenges

The target in its context

Cancer is a complex process in which many molecular and cellular processes change over time. The targets in a specific tumour that we attack today with targeted therapies, anti-angiogenesis or immunotherapy, change over time. What is a suitable target today may no longer be suitable tomorrow. After all, tumours are extremely successful in adapting themselves again and again by activating alternative cellular processes and developing resistance. Moreover, the tumour lives in a tumour environment that may also affect its growth, invasion and metastasis.

Effective treatment therefore requires not only additional research into supplementary targets, but also a better understanding of the relationships between the various cell types and tissues in and around a tumour, of the metabolic reactions that feed the tumour, of the way tumour cells break down certain drugs or render them harmless, and the mechanisms that control invasion and metastasis.

Better cancer models

As stated earlier, experimental animals still have key role in unravelling the fundamental biology of cancer (see 'Experimental animals in cancer research', page 28). They are also, however, indispensable in the development of new medicines: animal models are needed to study the efficacy, safety and proper dosage of new medicines, to determine the extent to which cancer cells develop resistance, to identify the mechanisms of action, etc. It would be ethically irresponsible to perform such initial experiments on patients with cancer. Consequently, no drug development is possible without a preclinical phase that uses animal models.

However, there is a problem in this respect: 92% of potential cancer drugs that have given favourable results in animal models fail in human clinical trials. The cause is our (temporarily) limited ability to replicate the complexity of the human cancer process, in all its aspects, in animal models. The generation of better clinical models continues to be a major challenge in cancer research.⁵⁰

These do not necessarily have to be animal models, however. Cellular models are also gaining strength. Consider, for example, organoids - small

3D organs that are grown in the laboratory and that resemble our own organs: their structure and biochemical functions have similarities with, for example, our liver, or blood vessels, or intestine, etc. They also allow human diseases to be examined 'in a dish' - in a test tube or culture dish.⁵¹ There are also unceasingly powerful computer models that can map interactions 'in silico' and which are gradually becoming indispensable in the development of new drugs. In this way, the use of test animals can be reduced. It is naturally a challenge to limit animal use and still obtain good cancer models.

Modified clinical studies

Biomarker-guided studies

Traditionally, clinical research involves three to four major phases, with increasing numbers of people taking part in each successive study phase (see 'The development of a medicine', page 56). Only when it has been proven that the new agent is superior to the standard treatment or is equivalent to it but gives, for example, fewer side effects or yields another benefit, is it approved by the government. In most cases, the drug is then prescribed to the whole group of patients suffering from the disease against which the drug has been developed.

In new cancer medicine, with more and more precision medicines, patients are pre-selected by means of biomarkers. That principle of pre-selection based on a biomarker profile is also being used increasingly during clinical studies. As a result, the studies become more focused and the success rate should increase.

Combination studies

But pre-selection of patients does not solve the resistance problem. By shooting at only one

target, the escape routes for the tumour remain wide open. So what is the solution? There are other examples from the field of medicine that show the way. Take HIV and AIDS. In that case, patients were also initially treated with only one medicine. The quantity of viruses in their blood dropped spectacularly only to rise again afterwards despite continued treatment. Resistance was also developing there. The answer to resistance in HIV was to give combinations of medicines from the start.

Combination therapy seems also the way to go in cancer. Except that with cancer it is very much the question which of the possible combinations of the hundreds of available drugs will be the most effective. For this we will have to design a type of clinical study that differs from the traditional phase III and phase IV studies with their thousands of participating patients. In oncology, that sort of large-scale monotherapy clinical studies will increasingly become a thing of the past. They will make room for smaller studies on well-selected subpopulations based on biomarker profiles, with a well-chosen mix of cancer drugs.⁵²

The first cancer therapies to combine multiple targeted medicines or combinations of targeted drugs with conventional therapies (chemotherapy and/or radiation) are now through the clinical study phase. Combination therapies are finding ever wider application in cancer care.

Collaboration and partnerships

To steer clinical cancer research in this direction, numerous hurdles have to be taken. Or, as the Brussels-based European Organisation for Research and Treatment of Cancer (EORTC) puts it: "The identification of new cancer drugs urgently requires a different approach. (...) The complexity

and cost of developing cancer drugs is now beyond the knowledge and operational capacity of individual organisations (even of the largest pharmaceutical companies - Ed.). This then

requires a radical departure from the traditional path of drug discovery and new forms of multidisciplinary partnerships and collaboration are needed to achieve success."⁵³

NEW PARTNERSHIPS FOR DEVELOPING NEW CANCER TREATMENTS

- *All relevant data about as many cancer patients as possible must be accessible and available for analysis in order to contribute to our current and future knowledge about cancer care and the outcomes of that care. This vision of a more systemic and integrated approach to cancer - which fits in with system biology as described in the section 'Research leads to new insights' - requires the collection, analysis and integration of an enormous amount of data. We may even have to assume in the future that every cancer patient will end up in one or more clinical studies. Realising this promise of 'big data' requires a stronger partnership between patients, patient organisations, doctors, researchers and those developing new cancer treatments.^a*
- *Pharmaceutical companies need to work together much more. For example, they will have to 'share' their medicines during clinical trials. After all, it will only rarely be the case that one company has all the medicines that are compared in a 'combination study'.^a*
- *The development of biomarkers linked to a treatment requires cooperation between pharmaceutical companies and companies that develop diagnostic tests. Moreover, the diagnostic and follow-up tests to monitor the treatment could be much more advanced in the future than the molecular tests we have today. It is quite possible that, for example, we will make much more use of metabolite profiles to monitor the evolution of a tumour.^{b,c}*
- *Oncological services from hospitals and research centres will have to collaborate much more in networks and share their data on patients and biomarker profiles. No hospital, not even a very large one, will be able to supply enough patients with a specific cancer and biomarker profile for the wide variety of studies that will be needed. This collaboration will also have to take place internationally and require the development of a digital platform to get the right patient, in the right hospital, in the right clinical study.^a*
- *Hospitals will, perhaps, specialise even further and develop their expertise in specific cancer domains instead of offering all cancer treatments. This trend towards sub-specialisation has already begun.*
- *Large academic research centres or consortia of centres can take a more prominent role, not only in the initial phase of medicines research - what is called the discovery phase - but also in the clinical studies phase (known as the 'development' phase). By conducting smaller, more focused clinical studies, the cost of these studies falls and come within reach of non-private research institutions.^{d,ef} Some argue frankly for an open innovation in which where public-private partnerships will play a much larger role.^{d,e}*
- *The government will have to invest more in practice-oriented clinical studies in areas that the commercial actors avoid but which are relevant for cancer patients, caregivers and policy makers.^f*

The cost of innovative medicines

A sore point is undoubtedly the cost of new cancer medicines. Treatments that cost many tens of thousands of Euros per year are no longer an exception. In principle, the price is determined by the cost of development and production, the size of the target group and the social added value of the medicine. As a result, medicines for small target groups and/or medicines with a large impact on the survival and quality of life of the patient are often very expensive.

The question is whether we can continue paying those prices, especially now that in the future combinations of precision medicines and possibly immunotherapies will be a solution for more and more patients. In 2015, 5% of the total Belgian medicines budget (around 4 billion Euro) was spent on innovative cancer treatments. A recent study predicts that this will increase to around 9% by 2020. This amounts to more than 500 million Euro. This would represent, in a period of only seven years, a tripling of the 2013 budget for cancer drugs.⁵⁴

Stefan Gijssels

"It is often said that cancer treatments are expensive, especially the medicines. Well, my total treatment has cost 60,000 Euro, of which only 5,000 Euro went on medicines. Today in Belgium we pay € 40 per capita per year for all the cancer medicines used. That doesn't seem too much to me."

Dirk Veldeman

"I don't have a problem with companies making a profit from on the medicines that they invented. Our society runs on profit, after all. That's what gets things done. Nevertheless, everyone has a social responsibility. Some of that profit must be ploughed back into research. If I was the CEO of a pharmaceutical company, I wouldn't be doing that purely for idealistic reasons but rather from far-sightedness. Because it's only by investing that can you make a profit in the future. That's how it goes. But, unfortunately, I never made it to the CEO level of a pharmaceutical company", says the retired journalist.

At various levels and in various circles, we are considering how we can guarantee the affordability of cancer treatments. Countries such as the United Kingdom impose a threshold price, above which a certain treatment is not reimbursed. The Netherlands also sometimes takes that course. Other countries are looking for more flexible solutions. For example, organising 'group purchases', where a group of hospitals, health insurers or health insurance funds jointly purchase medication. This strengthens their negotiating position and lowers the price.

Such a system can also be developed internationally, with a group of countries jointly negotiating the price of a medicine. Belgium, the Netherlands, Luxembourg and Austria already

do this for medicines for rare diseases and wish to expand this in the future. Another possibility is a 'pay for cure' contract with manufacturers. A medicine is only reimbursed if the patient actually benefits from it. If a patient does not benefit, the government does not pay and the manufacturer covers the costs. Other and increasingly diverse types of agreements are being concluded to reduce prices.

Nevertheless, many continue to wonder how cancer treatments can remain affordable in the future. In any case, this will only succeed if all those involved behave responsibly and consider the common interest over the long term.⁵⁵



The story of _____

ELS AND HARRY, FLO'S PARENTS

"Flo was allowed to go home that day. Four days after her brain surgery. When my husband and I arrived at the hospital at 12 o'clock, we were taken aside and were told that the tumour in Flo's head was malignant", says Els Bortier, wife of Harry De Geyndt and mother of Flo. "What was first described as a possible source of epilepsy, a vascular malformation, turned out to be a brain tumour. Somewhere between grades 2 and 3 - the doctors had not yet decided. Two hours later we were standing outside together with our ten year old daughter. That was it, then. We had to do it alone from there on."

"The communication between the hospital and us as parents was not always optimal", remembers Els Bortier. "The way Flo was told she had a new tumour, the date for a new operation, and especially the coordination and agreements between the doctors in the two hospitals during, and especially after, the immune therapy did not go well either. I know, this all happened more than 10 years ago; I hope that things are better organised now".

"At that time I had a strong feeling that these two hospitals and their doctors were involved in a kind of mutual competition", Harry adds, "but you still go along with things, because you want the best for your child. You really want your child to get better and heal. You will do everything for that.

Even treatments that are still very experimental and offer no guarantees." "After Flo's second operation, I realised that we would have a hard time as a family. The impact that a child with cancer has on a family is so indescribably large. As a parent, you deal with those problems in your own way, but you also have to respect each other", says Els. "Flo was also the youngest of three. Our other two children were also entitled to attention. They were struggling with their emotions too."

"I finally gave up my work as a pre-school teacher", says Els. "I wanted to be there for my family. For all my family. Not just for Flo. It is sometimes said that a disease like that tightens family bonds and makes it stronger. That's all very relative, you know. You are often completely alone. I feel that we've got too little relief and support. And don't forget the practical side of things: all the doctor's visits, in and out of the hospital, all the emotions ..."

"We are happy and grateful for what there is. Happy because we could and did fight for Flo."

"If I hadn't given up my job, our family might have fallen apart. Then we certainly wouldn't have been



as strong as we are now. We are happy and grateful for what there is. Happy because we could and did fight for Flo. But there were heavy moments. Of course, there are also good memories," says Els. "I sometimes organised surprises for Flo. Little things - but full of feeling. But also how Flo found her way in the playing and living area of the hospital's paediatric oncology department. The

activities and trips that the psychologist and game coaches organised ... Flo could enjoy that, but so could I as a mum, or even the whole family. Because other families were there, we felt like we weren't the only ones in this struggle. That feeling has stayed with us because the family still goes to the Children's Cancer Day in Planckendaal every year on the first Sunday in October. That's a fixed date for us."

"You feel both understanding and incomprehension in the people round you if you have a child with cancer", explain Els and Harry. "On the one hand there is a kind of incomprehension linked to ignorance. Nobody knows what it means, what you feel, the hell you go through. Only parents who have experienced this themselves can understand that. Only they know that world. The incomprehension of young people vis-a-vis Flo's difficulties in life and the social isolation that Flo had to deal with was painful to see. And yet, there were also people who continued to visit Flo and us. People who were not just around during the time of the first operation, but also for the fourth. With each operation, there were fewer, but the small group that remained did so much to keep us going."

"I really wanted to do something for a good cause", says Harry. "Something for Flo, but also for other cancer patients. A colleague at work came up with a crazy suggestion: a sponsored two-week bike ride from Brussels to Florence - appropriate for a daughter named Flo, isn't it? With the rest of our family we raised 10,000 Euro. Part went to 'The apple garden' - the playing and living area for the children with cancer at the University Hospital in Brussels - and a part went to 'Make a Wish'."

"Sometime in 2012, after Flo's fourth operation, I came in contact with the organization of the 1,000 kilometre race for Stand up against Cancer", continues Harry. "Starting with the third time of this event, I've been taking part as a solo rider. I ride the whole 1,000 kilometres myself. Well, I got the bug: the physical and mental challenge, the mission, the atmosphere, the solidarity between the participants." "Every year we collect 5,000 Euro", adds Els. "Especially with our family. We don't have a network from our professional life, like

many other participants do. So we have to collect money through events - a spaghetti party, wine sales ... you name it. We can count on the help of people who want to support our family and who want to stand up against cancer together with us every year."

"I really wanted to do something for a good cause. Something for Flo, but also for others."

Flo's parents think back with nostalgia to that time, two years ago, when Flo cycled the last part of the 1,000 kilometres. So much came out then. That doesn't leave you untouched. When Harry, together with Flo, darts over the cobblestones in Mechelen, on his way to the finish, so many images come flooding in: Flo in the hospital, Flo who was forced to grow up so fast, Flo who keeps on fighting, who struggles to find her way in life ... Harry: "Even after riding 1,000 kilometres, what you see is how your daughter with her curly blonde hair is exerting herself on her bike. How determined she is to get the finish, at any cost, with her iron will to continue. You're concerned, but also proud. Physically you are empty, but mentally you are full of energy." "Once she's through the finishing tape, Flo runs into my arms", remembers Els, "she lets out a yell from her innermost self ... that cry is forever engraved in my memory and heart. I still hear it ... as if she had put her entire life story together in that one cry."



8 Keep on fighting...

In the 1970s, Richard Nixon, the then President of the United States, announced 'The War on Cancer'. Almost 50 years have passed and the war against cancer is far from won. However, we are at the dawn of a new phase in the fight against cancer: thanks to new scientific insights, technological innovations and new therapies, the prospects for success are greater than ever. There is hope that we will eventually be able to control cancer, even though for now we will have to make do with the desire to turn cancer into a chronic disease that is no longer deadly. A disease for which the patient receives a continuous treatment that preferably generates as little burden as possible.

The human genome project and the resulting technologies have confirmed to us that cancer is originally a disease of the genome, of the DNA and that each tumour carries its own signature of DNA changes, which drives cancer growth. Although each tumour is, from a molecular perspective, unique and heterogeneous, there are certain reaction chains and cell systems that are repeatedly affected. These common features are also called the 'hallmarks' of cancer. They form the basis for research into new biomarkers and for medicines targeted at specific reaction chains.

Another rapidly developing research area looks beyond the tumour cell and focuses on the environment of the tumour. After all, healthy cells from that environment are manipulated, even hijacked, by the tumour cells to promote their own growth and to be able to metastasise. Un-

derstanding the interaction between the tumour and its environment can open the way to new treatments.

Powerful computers and new calculation methods make it possible to assemble, manage and analyse exponentially growing databases with molecular and clinical data. The use of 'big data' not only reveals unknown links, it is also crucial for generating predictive models of cancer progression and new therapeutic possibilities. However, it remains a challenge to integrate all these new developments into a coherent and integrative insight into the biology of cancer and to turn this into new therapeutic possibilities, in both early detection and screening and - especially - in successful prevention.

Never before have there been so many new drugs in the research pipeline. Sometimes these lead to unexpected success stories, although we always know that one swallow does not make a summer. We must continue to look for better therapeutic options in an open collaboration between patients, doctors, researchers, governments and industry. That requires patience, investment and perseverance ... to keep fighting against cancer.

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Thanks to close collaboration with the Flemish universities UGent (Ghent University), KU Leuven (University of Leuven), UAntwerp (University of Antwerp), Vrije Universiteit Brussel and UHasselt (Hasselt University), and a solid investment program, VIB combines the collective scientific expertise of all its research groups in a single institute. The results of that research are translated via technology transfer into concrete applications for society such as new diagnostics, medicines, treatment methods and agricultural innovations. These applications are often developed by young start-ups that have arisen from the VIB or through collaboration with existing companies. In this way, additional employment is created and we bridge the gap between research and entrepreneurship.

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